Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/575,522
Filing Date	April 12, 2006
First Named Inventor	Nafizal Hossain
Group Art Unit	1625
Conf No.	3659
Examiner Name	David K. O'Dell
Attorney Docket Number	06275-503US1

This is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. §1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s)
   - a. ☐ Previously submitted. If a final Office action is outstanding, any amendment filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on ______
     - ii. ☐ Other ______
   - b. ☒ Enclosed
     - i. ☒ Amendment/Reply
     - ii. ☐ Affidavit(s)/Declaration(s)
     - iii. ☒ Information Disclosure Statement (IDS)
     - iv. ☒ Other One Month Extension of Time
2. Miscellaneous
   - a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. §1.103(c) for a period of ______ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. §1.17(i) required)
   - b. ☐ Other ______
3. Fee The RCE fee under 37 C.F.R. §1.17(e) is required by 37 C.F.R. §1.114 when the RCE is filed.
   - a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 06-1050
     - i. ☐ RCE fee required under 37 CFR 1.17(e)
     - ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. ☒ Other Any deficiencies
   - b. ☐ Check in the amount of $______ enclosed
   - c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED

Name (Print/Type)	John T. Kendall, Ph.D.	*Registration No. (Attorney/Agent)*	50,680
Signature	John T. Kendall	*Date*	April 14, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nafizal Hossain	Art Unit	: 1625
Serial No.	: 10/575,522	Examiner	: David K. O'Dell
Filed	: April 12, 2006	Conf. No.	: 3659
Title	: NOVEL TRICYCLIC SPIRODERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY		

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PETITION FOR ONE-MONTH EXTENSION OF TIME

Pursuant to 37 CFR §1.136, applicant hereby petitions that the period for response to the action dated December 14, 2007, be extended for one month to and including April 14, 2008.

The fee in the amount of $120 for the one month extension fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-503US1.

Respectfully submitted,

Date: April 14, 2008

John T. Kendall

John T. Kendall, Ph.D.
Reg. No. 50,680

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nafizal Hossain	Art Unit	: 1625
Serial No.	: 10/575,522	Examiner	: David K. O'Dell
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INFORMATION DISCLOSURE STATEMENT

Applicants wish to bring to the Office's attention a Notice of Allowance that was issued in connection with co-pending and commonly owned application USSN 10/579,545, filed on May 16, 2006 (along with what appears to be the Examiner's search results from USSN 10/579,545). Applicants respectfully request that consideration of the above-discussed documents be acknowledged here or in the next written action or communication from the Office.

No fee is believed due as this Statement is being filed with a Request for Continued Examination. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-503US1.

Respectfully submitted,

Date: April 14, 2008

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nafizal Hossain	Art Unit	: 1625
Serial No.	: 10/575,522	Examiner	: David K. O'Dell
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AMENDMENT IN REPLY TO ACTION OF DECEMBER 14, 2007

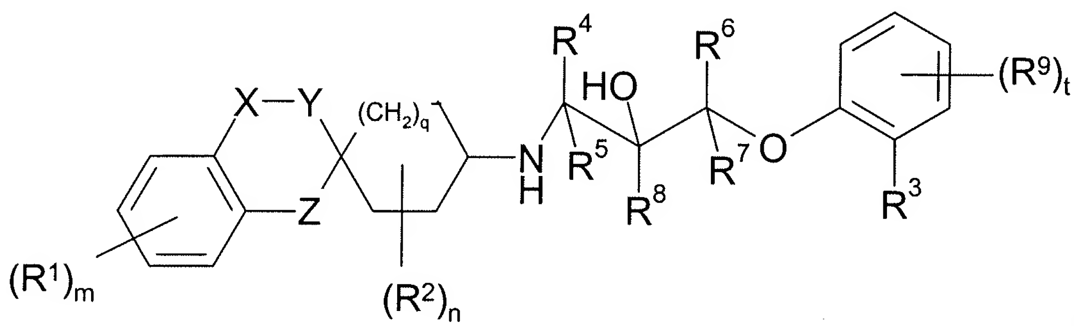
Please amend the above-identified application as follows:

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A compound of formula



(I)

wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy or sulphonamido;

~~either~~ X represents a bond; ~~and~~ Y represents -O-, ~~and~~ Z represents $-CH_2$;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

q is 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4, R^5, R^6, and R^7 ~~and R^8~~ -each ~~independently~~ represent a hydrogen atom;

R^8 represents a hydrogen or C_1-C_6 alkyl group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl;

R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{13}, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl,
(iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino, hydroxyl, C_1-C_6 haloalkyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylcarbonylamino and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur and optionally further comprising a bridging group, the ring being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl and C_1-C_6 haloalkyl, or (iv) C_1-C_6 alkylsulphonyl,

or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom and that is optionally fused to a benzene ring to form a 8- to 11-membered ring system, the heterocyclic ring or ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, amido, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylaminocarbonyl, di-

C_1-C_6 alkylaminocarbonyl, phenyl, halophenyl, phenylcarbonyl, phenylcarbonyloxy and hydroxydiphenylmethyl;

R^{12a} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents a C_1-C_6 alkyl, amino or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, C_1-C_6 alkylsulphonyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring that optionally further comprises a ring nitrogen, oxygen or sulphur atom, the heterocyclic ring being optionally substituted by at least one hydroxyl; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

or a pharmaceutically acceptable salt thereof.

2. (Original) A compound according to claim 1, wherein X and Y have the meanings shown in the following table:

X	Y
bond	O
O	bond
CH_2	bond
bond	CH_2

Claims 3-4 are cancelled.

5. (Previously presented) A compound according to claim 1, wherein R^3 represents $-NHC(O)R^{10}$ or $-C(O)NR^{11}R^{12}$.

6. (Previously presented) A compound according to claim 1, wherein t is 1 and R^9 is located in the *para* position with respect to R^3.

7. (Currently Amended) A compound according to claim 1 selected from:

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxy-*N*-methylbenzamide,

N-2-({(2S)-3-[5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-fluorophenyl]acetamide,

2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-*N*-methylbenzamide,

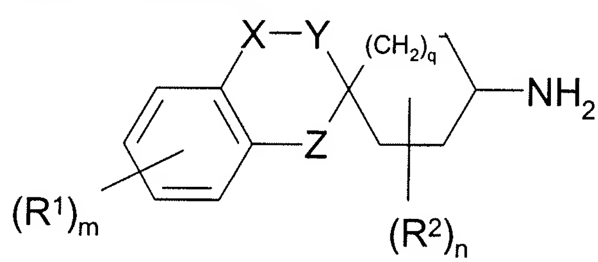
N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxypropyl}oxy)-4-hydroxyphenyl]acetamide,

N-[2-({(2S)-3-[(5-Chloro-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-4'-yl)amino]-2-hydroxy-2-methylpropyl}oxy)-4-hydroxyphenyl]acetamide (trifluoro acetate),

and pharmaceutically acceptable salts ~~and solvates~~ of any one thereof.

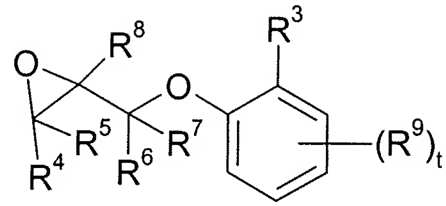
8. (Withdrawn) A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula



(II)

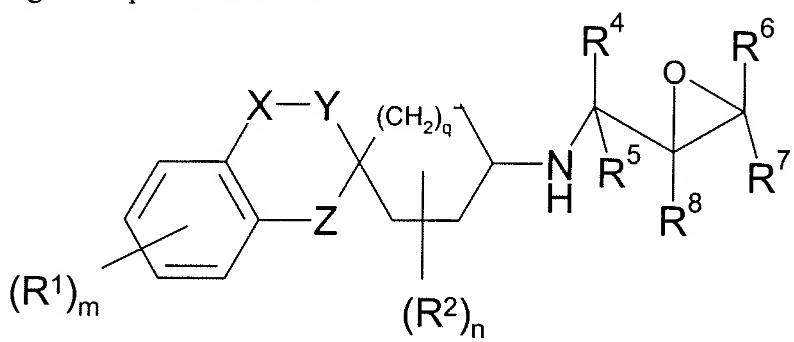
wherein m, R^1, n, R^2, q, X, Y and Z are as defined in formula (I), with a compound of formula



(III)

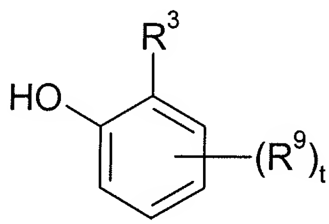
wherein R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

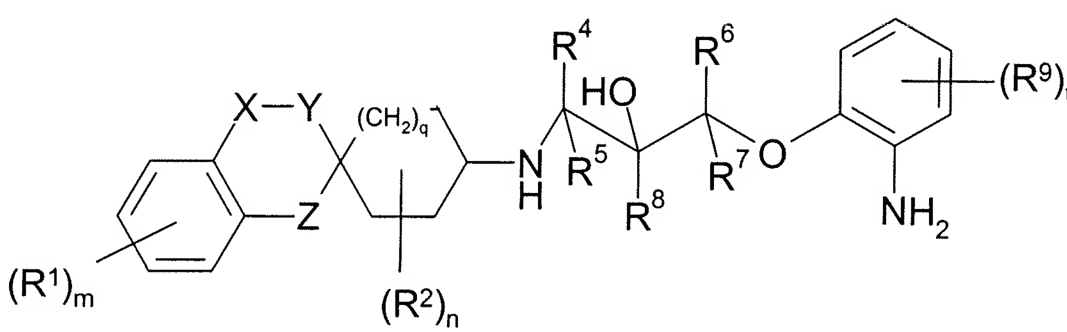
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of formula



(V)

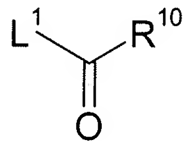
wherein R^3, t and R^9 are as defined in formula (I), in the presence of a suitable base; or

(c) when R^3 represents -NHC(O)R^{10}, reacting a compound of formula



(VI)

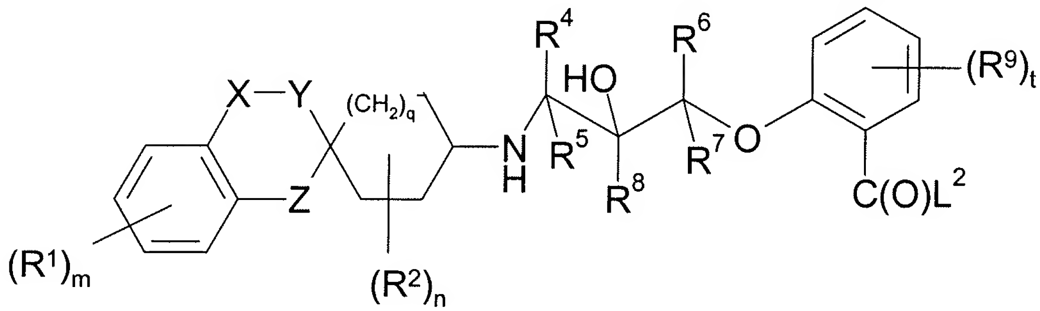
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula



(VII)

wherein L^1 represents a leaving group and R^{10} is as defined in formula (I); or

(d) when R^3 represents -C(O)NR^{11}R^{12}, reacting a compound of formula



(VIII)

wherein L^2 represents a leaving group and m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula (IX), NHR^{11}R^{12}, wherein R^{11} and R^{12} are as defined in formula (I); or

(e) when R^3 represents -NHC(O)R^{10}, R^{10} represents –NR^{14}R^{15} and R^{14} and R^{15} both represent hydrogen, reacting a compound of formula (VI) as defined in (c) above with potassium cyanate;

and optionally after (a), (b), (c), (d) or (e) forming a pharmaceutically acceptable salt or solvate.

9. (Previously Presented) A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. (Withdrawn) A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable

salt or solvate thereof as claimed in claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. (Cancelled)

12. (Withdrawn) A method of treating a disease or condition in which modulation of chemokine receptor activity is beneficial, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

13. (Withdrawn) A method of treating rheumatoid arthritis, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

14. (Withdrawn) A method of treating chronic obstructive pulmonary disease, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

15. (Withdrawn) A method of treating asthma, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

16. (Withdrawn) A method of treating multiple sclerosis, the method comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

17. (Withdrawn) A method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

18. (Withdrawn) A method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt ~~or solvate~~ thereof as claimed in claim 1.

REMARKS

Claims 1-10 and 12-18 are pending. Applicants have cancelled claims 3 and 4 without prejudice. Claims 1, 2, 5-10, and 12-18 will therefore be pending upon entry of the proposed amendments.

Support for the amendment to claim 1 can be found throughout the specification, e.g., at page 8, lines 21-22.

Office's response to arguments presented in previous reply

The Office Action states, in part, on page 2 (emphasis added):

> The rejection for scope of enablement are maintained as the directions for the preparation and use of the compounds commensurate in scope with the claims has not been provided. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again vide infra). **It would appear that the applicant is arguing that essentially any molecule, even molecules of unknown structure, can be made without undue experimentation.**

Applicants wish to address the underlined portion of the above-quoted passage from the Office Action. Applicants did not take the position that "essentially **any** molecule, even molecules of **unknown** structure, can be made without undue experimentation" (Office Action, page 2, emphasis added). Rather, Applicants argued that a person of ordinary skill in the art, given the present specification as a guide and the ability to modestly experiment, could make and use the compounds encompassed by the present claims without undue experimentation. Further, since the skilled person could readily discern which chemical structures fall within the claimed genus and which do not, there are no "molecules of unknown structure" encompassed by the present claims.

Maintained Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-6 and 9 remain rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The rejection includes a number and variety of supporting information, such as quotations from a recent treatises on organic synthesis and results of a search of the Aldrich Chemical Company catalog. Applicants will therefore begin by summarizing some of the points and information raised throughout the rejection.

[1] Brief Synopsis of Rejection

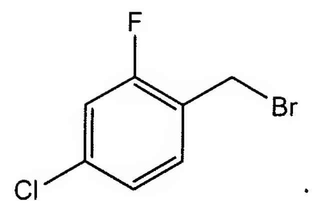
[A] The rejection begins by stating, in part (Office Action, page 11):

> [T]he specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make of use the invention commensurate in scope with these claims.

This statement is followed by a brief review of the so-called Wands (*In re Wands* 858 F.2d 731) factors.

[B] Next, the Office provides a composite reaction scheme (see Scheme 1 on page 14 of the Office Action), which apparently is intended to show the starting materials and intermediates used to prepare the title compound of Example 1 in the specification[1]. The Office then indicates that it conducted a search to determine whether some of these starting materials and intermediates were commercially available. It appears that this search was limited to a search of the Aldrich Chemical Company ("Aldrich") catalog. One of the starting materials that was searched was 2-(bromomethyl)-4-chloro-1-fluorobenzene, the structure of which is shown below:

[1] Applicants respectfully point out that compound **6** in Scheme 1 on page 14 of the Office Action should show the chemical structure of *p*-methoxybenzyl chloride rather than *p*-methoxybenzoyl chloride (i.e., the structure should not have a carbonyl group; see specification at page 28, lines 23-24).



According to the Office's search results, Aldrich does not, at the present time, appear to sell 2-(bromomethyl)-4-chloro-1-fluorobenzene.

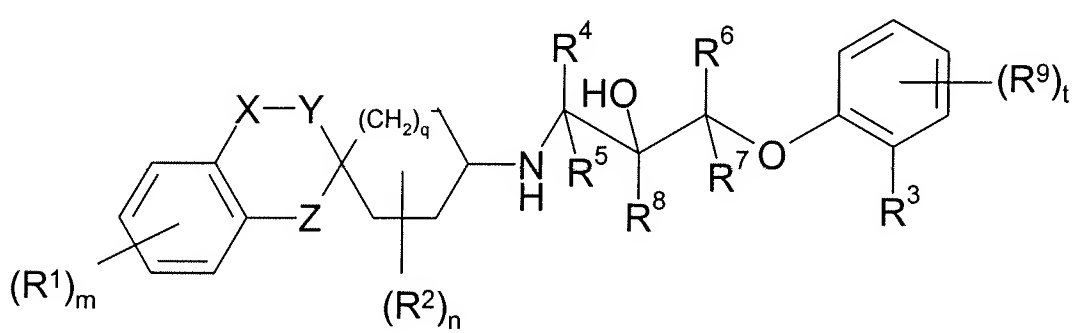
[C] The Office Action then goes on to state:

> If such starting materials could be obtained ... it is very clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by Grignards [citation omitted]. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur [citation omitted]. The "alkylhalo" compounds will undergo metal exchange when in the presence of a Grignard (Knochel ibid.).
>
> Another disturbing feature of what is before the examiner, is the fact that is appears that no assays were performed.

This is respectfully traversed.

[2] The Claimed Compounds

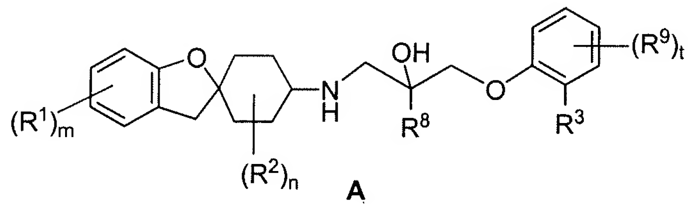
Claim 1 is directed to compounds having formula (I):



(I).

The claims in their present (and previously presented form) require that X must be a bond, Y must be -O-, Z must be $-CH_2$; q must be 1; and R^4, R^5, R^6, R^7 must each be a hydrogen atom.

As such, the claimed compounds are required to have the following core structure (referred to throughout as formula (A)):



A

For the convenience of the Office, the remaining permitted points of variability on the core structure are set forth below:

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy or sulphonamido;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

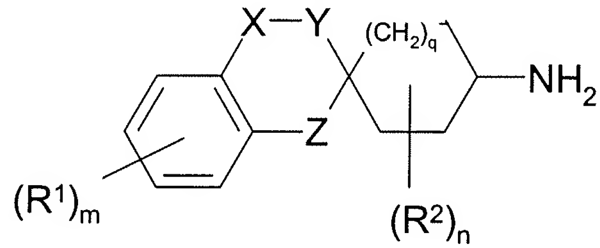
R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^8 represents a hydrogen or C_1-C_6 alkyl group;

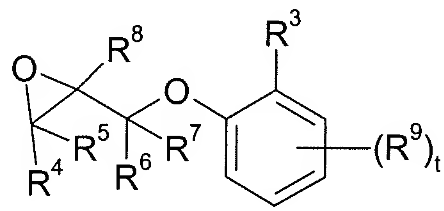
t is 0, 1 or 2; and

each R^9 independently represents halogen, cyano, hydroxyl, carboxyl, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl."

[3] The specification at page 19, line 18 through page 22, line 14 provides various processes for synthesizing the core structure required by the present claims (as well as the other core structures encompassed by the claims as originally filed). For example, the specification teaches that the claimed core structures can be obtained by reacting a primary amine having formula (II) with an epoxide having formula (III). See page 19, line 21 through page 20, line 3.



(II)



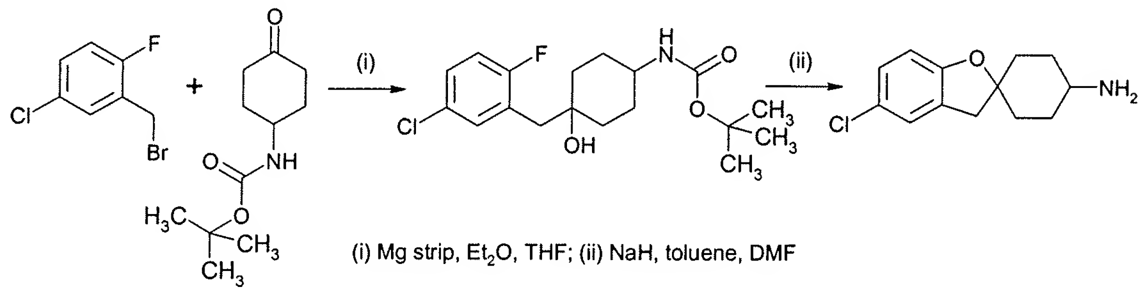
(III)

As another example, the claimed core structures can also be obtained, e.g., by reacting an epoxide of formula (IV) with a phenol of formula (V) (formulas not shown, see specification at page 20, lines 4-8). As a further example, a process is taught for installing an amide or reverse amide (i.e., the substituent corresponding to R^3) on the right most phenyl ring in formulas (I) and (A) (see specification at page 20, line 9 through page 21, line 12).

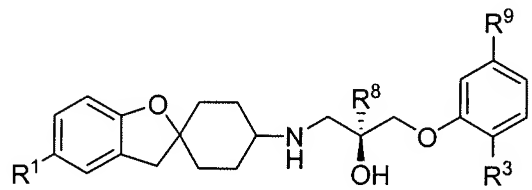
The specification goes on to disclose that the starting materials and other reagents were, as of Applicants' filing date, "commercially available, known in the literature, or may be prepared using known techniques" (specification at page 22, lines 2-3). In addition, detailed synthesis information (solvents, reagents, reaction temperatures, use of protecting groups) for the process steps is also provided. See specification at page 21, line 17 through page 22, line 3.

There is ample disclosure showing that the processes and guidance described above can be applied to the synthesis of compounds having the core structure required by the present claims. See, for example, the working example beginning at page 27, line 4, which shows the

synthesis of a representative amine of formula (II) from a commercially available benzyl bromide and a commercially available cyclohexanone:



See also Examples 1-5, which describe the synthesis of the following compounds:



Example	R^1	R^3	R^8	R^9
1	Cl	-C(O)NHMe	H	OH
2	Cl	NHAc	H	F
3	Cl	-C(O)NHMe	H	H
4	Cl	NHAc	H	OH
5	Cl	NHAc	Me	OH

As such, a person of ordinary skill in the art, using the knowledge he or she has, using the tools of chemistry, and guided by the Specification, could make the claimed compounds without undue experimentation.

[4] Before addressing the present rejection, Applicants first wish to discuss some of the relevant case law pertaining to the enablement requirement of 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, first paragraph provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, ...

I. The law does not require that every species of a genus be shown by a working example (even in the so-called unpredictable arts). To require this would limit the Applicant merely to what he or she has already done.

A. In fact, the Court of Customs and Patent Appeals (CCPA) in *In re Robins* 166 USPQ 552, 555 (1970) held that disclosure of representative compounds of a claimed genus is not even a requirement of § 112 (emphasis in original):

> Both the examiner and the board seem to have taken the position that in order to 'justify,' as the examiner said, or to 'support,' as the board said, broad generic language in a claim, the specification must be equally broad in its naming, and use in examples, of representative compounds encompassed by the claim language. This position, however, misapprehends the proper function of such disclosure. Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. … [R]epresentative examples are not required by the statute and are not an end in themselves. Rather they are a *means* by which certain requirements of the statute may be satisfied.

B. The CCPA in *In re Angstadt and Griffin* 190 U.S.P.Q. 214, 218 (1976) held that (emphasis in original) " appellants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art." As the Court explained (*Id.* at 218, italic emphasis in original; bolded underline emphasis added):

> Appellants have apparently not disclosed *every* catalyst which will work; they have apparently not disclosed *every* catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands'[2] of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. **<u>This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed</u>**. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides.'

In *Angstadt*, the appealed claims were directed to methods of catalytically oxidizing secondary or tertiary alkylaromatic hydrocarbons to form the corresponding hydroperoxides. *Angstadt's* methods included contacting the hydrocarbon with a complex catalyst consisting of a transition metal salt and a phosphoramide. The Court noted that *Angstadt's* application disclosed "a large but finite list of transition metal salts" (*Id.*), but also pointed out that "Appellants have actually carried out 40 runs using various transition metal salts and hexaalkyl-phosphoramides" (*Id.*). The Court concluded (*Id.*):

> If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. One skilled in this art would merely have to substitute the correct mass of a transition metal salt for the transition metal salts disclosed in appellants' 40 runs. Thus, we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst

complexes within the scope of the claims work to produce hydroperoxides and which do not.

It is further noted that the Court arrived at this conclusion even in view of the fact that "one of these examples yields no hydroperoxides in the final product. Also, appellants have expressly indicated in their specification that some of these organometallic complex catalysts 'yield * * * no hydroperoxides in the final product'" (*Id.*).

See also *Regents of University of California v. Eli Lilly & Co.* 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) (underline emphasis added):

> This is analogous to enablement of a genus under § 112, ¶ 1, **by showing the enablement of a representative number of species within the genus**. See *Angstadt*, 537 F.2d at 502-03, 190 USPQ at 218 (deciding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process);

In general, one can rely on the disclosure of representative compounds to satisfy the enablement requirement of § 112, first paragraph for a claimed genus. However, even in the unpredictable arts, one need not disclose every species encompassed by a genus to enable a claim to that genus.

II. "Patents are written by and for skilled artisans"[2]

A. The Federal Circuit discussed the enablement requirement of 35 U.S.C. § 112, ¶1 in *In re Buchner* 18 USPQ2d 1331, 1332 (1991) (bolded underline emphasis added, italics in original):

> In order to be enabling under 35 U.S.C. § 112, a patent application must sufficiently disclose an invention to enable those skilled in the art to make and use it. **The specification need not disclose what is well known in the art**. *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

---

[2] *See Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999).

The quote in *Buchner* later points out that an applicant is permitted, under the provisions of the statute, to exclude from his or her Specification information that is known in the art.

Accordingly, the fact that the specification does not disclose certain information, does not make a disclosure non-enabling. Evidentiary weight must be given to what was known in the art as of the applicants' filing date.

B. Subsequent to *Buchner*, the Federal Circuit, in *AK Steel v. Sollac* 68 USPQ2d 1280, 1287 (Fed. Cir. 2003)(emphasis added), considered the requirements for an enabling disclosure in view of *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988), which is relied upon by the Examiner in the 35 U.S.C. § 112, first paragraph rejections of record:

> The enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation. *Wands*, 858 F.2d at 736-37. ... **That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps**, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending on the predictability of the art. *See Genentech, Inc. v. Nordisk A/S*, 108 F.3d 1361, 1366 [42 USPQ2d 1001] (Fed. Cir. 1997) ('[A] specification need not disclose what is well known in the art.'); see also *Wands*, 858 F.2d at 736-37 ('Enablement is not precluded by some experimentation, such as routine screening'). ... The question more precisely here is whether, with AK Steel's patent specification as an initial guide, the hypothetical skilled artisan's knowledge of the surrounding art and ability to modestly experiment would have been sufficient to enable him to make and use a steel strip containing a Type 1 aluminum coating, with the claimed wetting attributes at the time of the '549 patent's effective filing date in 1986 (*AK Steel* at 1287).

See also, *Amgen Inc. v. Hoechst Marion Roussel Inc.* 65 USPQ2d 1385, 1400 (Fed. Cir. 2003) (emphasis added), where the Court reasoned:

> The specification need **not** explicitly teach those in the art to make and use the invention; **the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation'** *[citations omitted]*.

Accordingly, the fact that a Specification does not disclose certain information does not make a disclosure non-enabling. Rather, the enablement inquiry must focus on whether a person

of ordinary skill in the art, given his or her knowledge of the prior art and the ability to modestly experiment, could bridge any gaps between the breadth of the disclosure and the breadth of the claims.

C. See also, *S3 Inc. v. nVIDIA Corp.* 59 USPQ2d 1745, 1749-50, (2001), where the Federal Circuit explained (bolded underline emphasis added):

> The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. *See Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ('**patents are written by and for skilled artisans'). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader**.

III. Enablement is not precluded by experimentation as long as it is routine experimentation and not undue experimentation.

A. The Federal Circuit discussed the "purpose" of the enablement provision in *Scripps Clinic & Research Foundation v. Genentech, Inc.* 18 USPQ2d 1001, 1006 (2001):

> The purpose of this provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art.

See also the Federal Circuit's discussion of the purpose of the enablement requirement in *Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.* 418 F.3d 1326, 1336-1337 (2005) (underline emphasis added):

> The purpose of this requirement is to ensure that 'the public knowledge is enriched by the patent specification to a degree **at least commensurate with the scope of the claims**.' *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed.Cir.1999); see also Donald S. Chisum, 3 Chisum on Patents § 7.01 (2002).

The Federal Circuit in *Warner-Lambert* stressed that the specification must teach one how to make and use the claimed invention without undue experimentation (*Id.* at 1337, emphasis added):

> Accordingly, we have held that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *[citations omitted]* 'The key word is 'undue,' not experimentation." *Wands*, 858 F.2d at 737 (citation omitted). **That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation**. See, e.g., *Nat'l Recovery Techs.*, 166 F.3d at 1196 ('The scope of enablement ... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.'); *Wands*, 858 F.2d at 736-37 ('Enablement is not precluded by the necessity for some experimentation such as routine screening.').

It is well settled that enablement is not precluded by experimentation. In other words, the enablement inquiry does not turn on whether experimentation may be needed to practice the claimed invention. Rather, the enablement inquiry turns on whether the amount of experimentation needed to practice the claimed invention is undue. *See, e.g., In re Angstadt and Griffin*, 190 USPQ 219 ("The key word is 'undue' and not 'experimentation.'").

B. The amount of experimentation can even be considerable, provided that it is routine and not undue. *See, e.g., Johns Hopkins University v. Cellpro, Inc.* 47 USPQ2d 1705, 1719 (Fed. Cir. 1998):

> Such routine experimentation does not constitute undue experimentation: 'The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.' *[citations omitted]*.

See also, e.g., In re Wands 8 USPQ2d 1400, 1404 (Fed. Cir. 1988, emphasis added) ('Enablement is not precluded by some experimentation, such as **routine** **screening**').

[5] The Federal Circuit in *In re Wright* 27 USPQ2d 1510, 1513 (1993) discussed the requirements for rejecting a claim under the enablement requirement of 35 U.S.C. § 112, first paragraph:

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

Applicants submit that the Office has not met this burden for any of the following independent reasons.

[6] The rejection appears to ignore the fact that the enablement inquiry **must** focus on whether a person of ordinary skill in the art, **given his or her knowledge of the prior art and the ability to modestly experiment**, could bridge any gaps between the breadth of the disclosure and the breadth of the claims.

[A] The present claims are directed to compounds that all share common and substantial structural attributes-- they are all required to have the same core structure (see formula (A) *supra*), and the specification provides ample guidance and direction for making this core structure and hence the claimed compounds (*vide supra*).

The Office's apparent concern regarding the (commercial) availability of 2-(bromomethyl)-4-chloro-1-fluorobenzene from Aldrich ("[m]ost disturbingly, we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made." Office Action, page 18) is misplaced for any one of the following independent reasons.

First, there is no legal requirement (or requirement in the specification or claims) that the claimed compounds must be made from commercially available starting materials.

Second, the compound in question was indeed commercially available as of Applicants' filing date.

Third, the Office's search was limited to only **one** vendor (Aldrich). The fact that the compound in question was not available from Aldrich would not have led the skilled artisan to reasonably conclude that the compound was not commercially available (or otherwise

unavailable by other means, such as conventional organic synthesis). In fact, Applicants were able to locate eleven current commercial suppliers of 2-(bromomethyl)-4-chloro-1-fluorobenzene by searching the ChemACX database provided by CambridgeSoft.

Finally, according to the Office, Aldrich does in fact sell (at least) fourteen 2-(bromomethyl)-1-fluorobenzenes that could be used to prepare some of the claimed compounds (see the chemical structures delineated on pages 15-18 of the Office Action). Thus, if anything, the Office's search results weigh on the side of Applicants' disclosure being enabling.

[B] Applicants now turn to the Office's comments summarized in paragraph **[1]**, **[C]** above, namely:

> If such starting materials could be obtained ... it is very clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by Grignards [citation omitted]. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur [citation omitted]. The "alkylhalo" compounds will undergo metal exchange when in the presence of a Grignard (Knochel ibid.).
>
> Another disturbing feature of what is before the examiner, is the fact that is appears that no assays were performed.

The specification states that "certain protecting groups ... may need to be protected by protecting groups" (specification at page 22, lines 5-13). The skilled artisan would recognize that the issues raised above (if in fact they presented themselves) could be addressed, for example, by the use of protecting groups as taught by the specification. The skilled artisan would also recognize that a desired functional group could also be introduced at a different stage in the synthesis so as to avoid being exposed to potentially incompatible reaction conditions. Protection and deprotection of functional groups and functional group manipulation were within with the skill of the art as of Applicants' filing date and, at most, fall within the purview of routine experimentation, which does **not** preclude patentability. Moreover, The fact that the specification does not disclose such known (and arguably well known) methods and materials does **not** make Applicants' disclosure non-enabling. *See S3 Inc. v. nVIDIA Corp.* 59 USPQ2d 1745, 1749-50, (2001):

> ('[P]atents are written by and for skilled artisans'). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader.

That being said, even if one or more of the claimed compounds could not be prepared (and Applicants do not concede that this is the case here), that does not render the claims unpatentable. The claims need not exclude inoperative embodiments. As the Federal Circuit explained in *Atlas Powder Co. v. E. I. Du Pont De Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude ... possible inoperative substances..." *Atlas Powder* at 414.

Finally, there is no legal requirement that the specification include biological data for the claimed compounds (in fact, there is no legal requirement that the specification provide working examples at all).

[7] The Office also appears to have taken the position that Applicants have enabled only those compounds that they have expressly disclosed and reduced to practice. This is evidenced by the above-quoted passages from the present Office Action, e.g., at page 11:

> [T]he specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents.

This is respectfully traversed. First, as discussed elsewhere, to enable a claim to a genus, one need **<u>not</u>** disclose and test every species encompassed by the genus, even in the so-called unpredictable arts. To require as such would limit the Applicants merely to what he or she has already done. Again, this is not the law. *See, e.g., In re Angstadt*, 190 USPQ 214, (CCPA 1976). See also MPEP § 2164.02: "[b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments." Put simply, the law provides that one can enable a genus under § 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

Finally, the enablement requirement also serves to advance the art to which the invention pertains. Applicants have provided the art with, *inter alia*, the knowledge that the claimed compounds modulate chemokine receptor activity. How is the art significantly or even incrementally benefited by requiring the Applicants to make and test additional compounds? Again, to require as such is effectively restricting the Applicants to claim only what they have done. This is unreasonable and is certainly not the law.

In summary, a person of ordinary skill in the art, using the knowledge he or she has, using the tools of chemistry, and guided by the Specification, could make the claimed compounds without undue experimentation.

In view of the foregoing, Applicants respectfully request that the 35 U.S.C. § 112, first paragraph rejection be reconsidered and withdrawn.

Rejections on the ground of nonstatutory obviousness-type double patenting

[1] Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 and 10 of USSN 10/579,545 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 5).

Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of USSN 10/581,171 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 9).

Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, and 14 of USSN 10/583,468 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, page 9).

Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 13 of USSN 10/520,699 "in view of Xue et al. U.S. Pre-Grant Publication 2006/0252751" (Office Action, pages 9-10).

This is respectfully traversed.

[2] The Federal Circuit discussed the requirements for establishing a *prima facie* case of obviousness for a claimed chemical compound in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 135x (emphasis added):

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).
>
> We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *Dillon*, 919 F.2d 688;*Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984)).
>
> [5] That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, **the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination**. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* **Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound**.

[3] The skilled artisan reading the claims of any of the foregoing applications (alone or in combination with Xue et al.) would not have been led to modify the claims of any of the foregoing applications in the manner needed to arrive at the presently claimed compounds. Indeed, the necessary modifications are precluded by (and therefore not even encompassed by) the claims of any of the foregoing applications. In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

[4] Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9, and 11 of USSN 11/744,659 (Office Action, page 10).

Claims 1-7 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9, and 11 of USSN 11/744,677 (Office Action, page 10).

This is respectfully traversed.

Each of USSN 11/744,659 and USSN 11/744,677 is a **divisional** application that claims priority to the present application. Moreover, the presently pending claims in both USSN 11/744,659 and USSN 11/744,677 are directed to subject matter that: (i) was subject to restriction by the Office in the present application; and (ii) was not elected by Applicants for prosecution in the present application (i.e., withdrawn subject matter). As such, both applications should be shielded from obviousness-type double patenting by the safe harbor provided by 35 U.S.C. § 121. Applicants therefore request further clarification as to how *In re Schneller* supercedes this provision of 35 U.S.C. § 121.

The fee in the amount of $120 for the one month extension fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-503US1.

Respectfully submitted,

Date: April 14, 2008

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/575,522	Applicant(s) HOSSAIN, NAFIZAL
	Examiner David K. O'Dell, Ph.D.	Art Unit 1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _30 April 2007_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-10 and 12-18_ is/are pending in the application.

4a) Of the above claim(s) _8,10 and 12-18_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1-7 and 9_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _12 April 2006 & 9 March 2007_.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10, 12-18 are pending in the current application.

2. This is a National Stage of PCT/SE2004/001476, filed October 14, 2004, which claims priority to Swedish Application Serial No. 0302755-4, filed October 17, 2003.

Applicant's Response to Restriction/Election

3. Applicant's election without traverse of Group I in the reply filed on April 30, 2007 is acknowledged.

Group I, Claims 1-7, 9 drawn to compounds and compositions possessing a spirocyclic benzofuran-cycohexyl core, where in applicant's Markush structure of Formula I X is a bond, Y is O, Z is CH_2, q is 1, $R_2=R_4=R_5=R_6=R_7=H$ shown as structure **I** in Figure 1.

This requirement is made final. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai; In re Brouwer and 35 U.S.C. §103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended

during prosecution to require the limitations of the product claims. Applicants are reminded of propriety of process of use claims in consideration of the "reach-through" format, which is drawn to mechanistic, receptor binding or enzymatic functionality. Reach-through claims are considered lacking of descriptive and enabling support from the specification. Thus, rejoinable process of use claims are those with particular disease named with efficacy support from the specification for treating the particular disease. This application contains claims drawn to an invention nonelected without traverse in the reply filed on April 30, 2007. A complete reply to this rejection must include cancellation of nonelected claims or other appropriate action

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

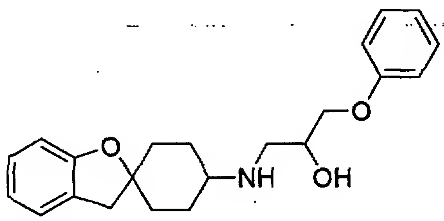
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-7, 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xue et. al. U.S. Pre-Grant Publication 2006/0252751 and Hossain, Nafizal; Ivanova, Svetlana; Mensonides-Harsema, Marguerite U.S. Pre-Grant Publication US 2005/0245741 A1. (USSN-10/520 699) The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

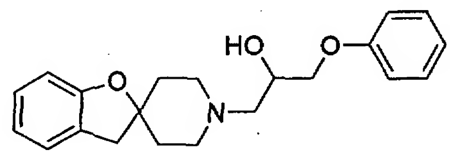
Determination of the scope and content of the prior art

(MPEP 2141.01)

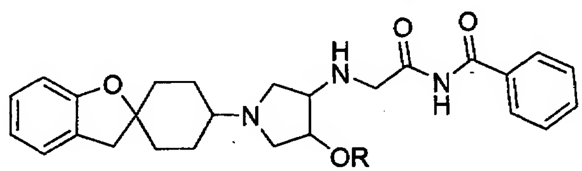
Xue et. al. teaches spiro[benzofuran-2,1'-cyclohexan]-4'-amines that are chemokine antagonists. Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite teach spiro[benzofuran-2,4'-piperidines bearing a 1-phenoxy-3-propan-2-ol substituent on the piperidinyl nitrogen atom. This relationship is illustrated graphically in Figure 1.



Instant case



U.S. Application 10/520,699
2005/0245741

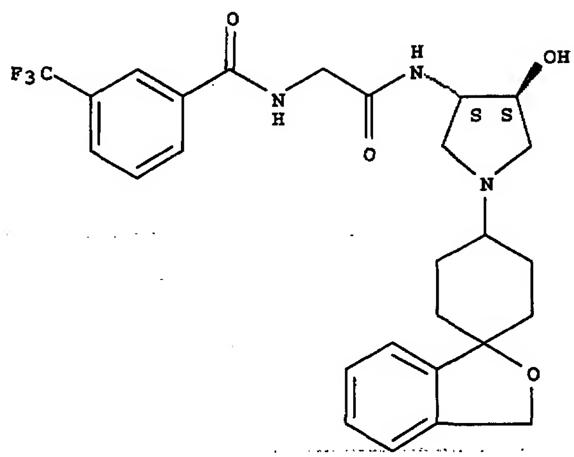


Xue et. al.

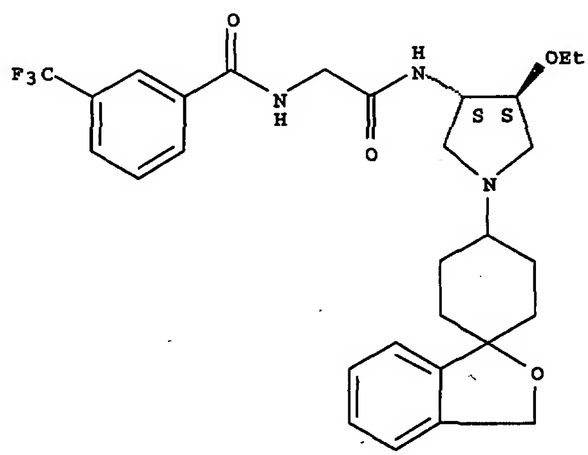
Figure 1. Structures of compounds that form the basis of the obviousness rejection as compared to the instant invention.

Some of the compounds disclosed by Xue are show below:

Registry #: 709018-09-7



Registry #: 709019-00-1



Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene group. By inserting a what is formally a methylene (CH_2 actually CH in the ring and H on N) into the compounds of Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite a

spiro[benzofuran-2,1'-cyclohexan]-4'-amine is produced, which is a core pharmacophore of chemokine antagonism. These relationships are illustrated graphically in Figure 2.

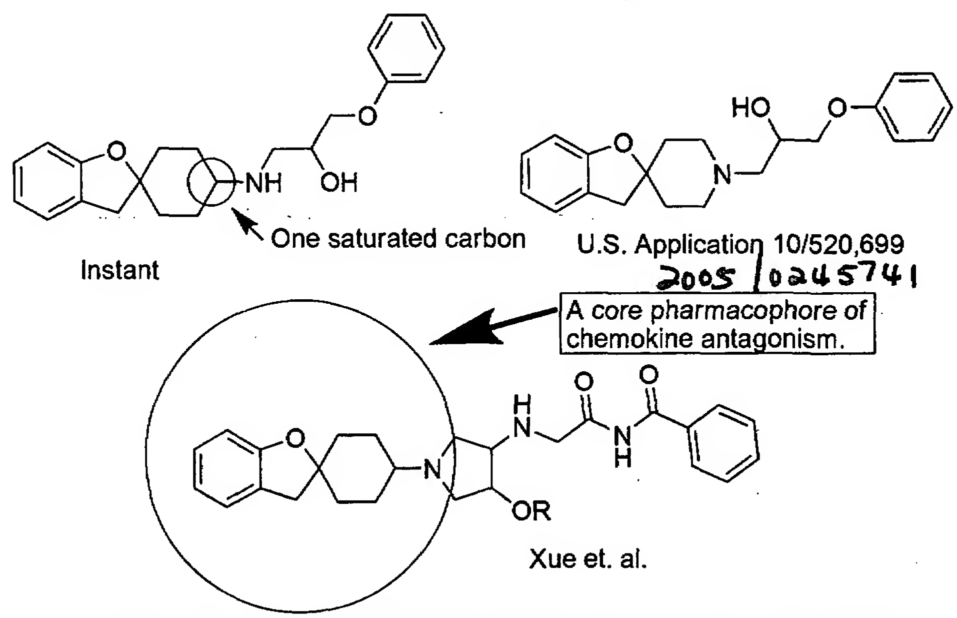


Figure 2. The differences between the compounds of the instant case and those of the prior art.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the

teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10 of copending Application No. 10/579,545 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here.

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12 of copending Application No. 10/581,171 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. This is a provisional obviousness-type double patenting rejection.

7. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, 14 of copending Application No. 10/583,468 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. Although claim 9 is apparently a claim for “a claim”.

8. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13 of copending Application No. 10/520,699 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here.

This is a provisional obviousness-type double patenting rejection.

9. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claim 1-7, 9, 11 of commonly assigned copending Application No. 11/744,659. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

10. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-7, 9, 11 of commonly assigned copending Application No. 11/744,677. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant

application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;

(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*
(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) **The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually

> looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work......Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)...................." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim IX Preface.

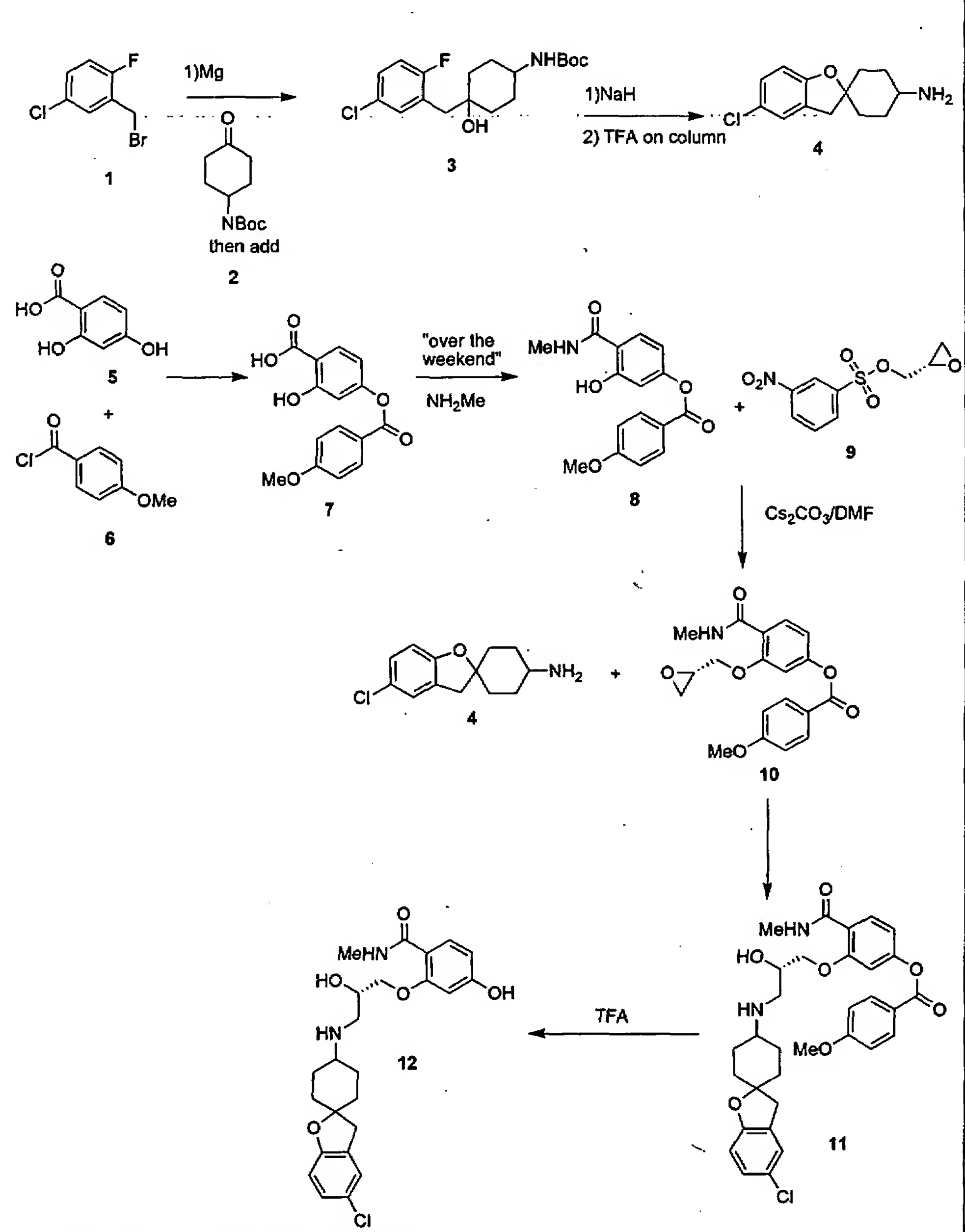
(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily

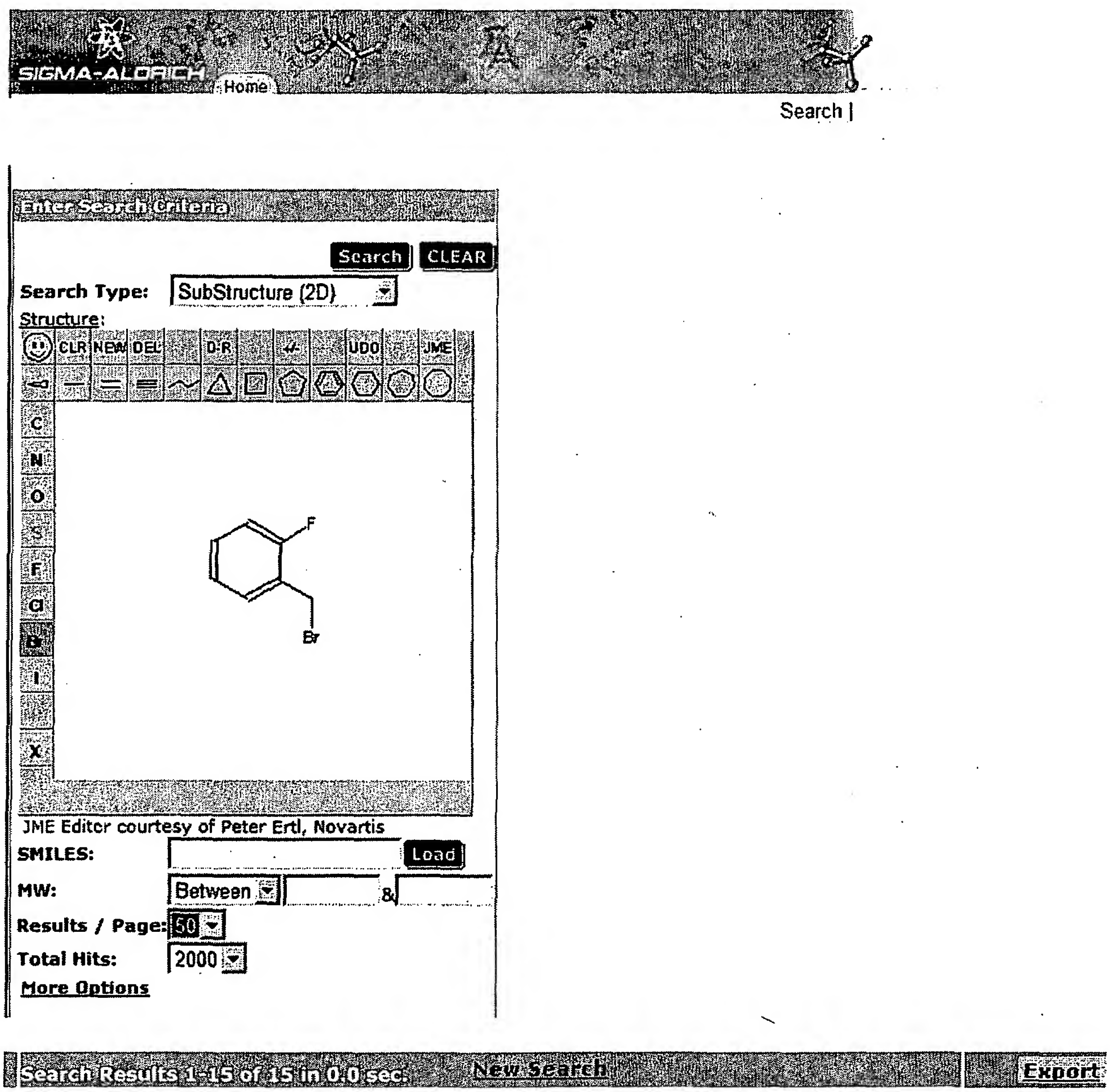
available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The synthetic route and starting materials that the applicant has provided to make the scope of this invention has been reproduced below as Scheme1:



Scheme 1. The chemistry relied on to construct applicant's compounds.

The key materials here are the α-bromo-2-fluoro-toluene derivative **1**, the N-Boc-4-amino cylcohexanone **2**, phenols such as **8** bearing amide groups, and glycidols **9**. A search for each of these materials in the Aldrich Chemical Company catalog (St. Louis, MO) was conducted, the reulsts of which are reproduced below:

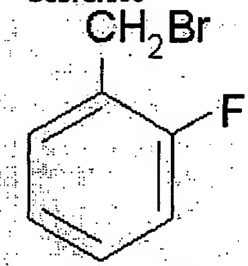


Sort By: MW

Compound Properties | Structure | Add | Prod. # | Purity

Name: 2-Fluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2-fluorobenzene
MF: C_7H_6BrF
CAS #: 446-48-0
MW: 189.02
MDL #: MFCD00000324
BP: 84 - 85 °C
FP: 181
d: 1.5670

Score:100

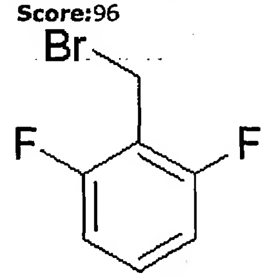


Zoom In

209511 98%

Name: 2,6-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 85118-00-9
MW: 207.02
MDL #: MFCD00000329
FP: 230

Score:96

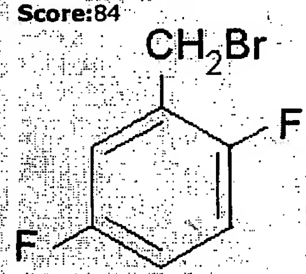


Zoom In

83141 purum, ≥95.0% (GC)
264431 97%

Name: 2,5-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,4-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 85117-99-3
MW: 207.02
MDL #: MFCD00009897
FP: 60
d: 1.6090

Score:84

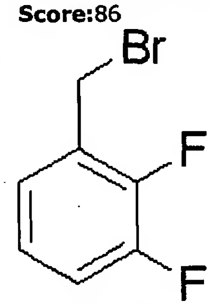


Zoom In

264423 98%

Name: 2,3-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 113211-94-2
MW: 207.02
MDL #: MFCD00042488
FP: 194
d: 1.6280

Score:86

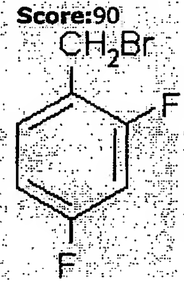


Zoom In

68318 ≥99.5% (GC)
74259 purum, ≥99.5% (GC)
265314 98%

Name: 2,4-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,4-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 23915-07-3
MW: 207.02
MDL #: MFCD00011649
FP: 104
d: 1.6130

Score:90

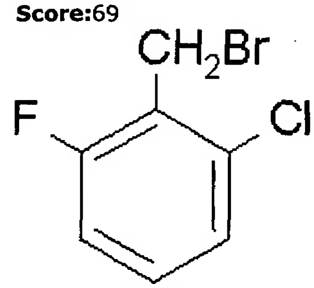


264415 98%

Zoom In

Name: **2-Chloro-6-fluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1-chloro-3-fluorobenzene**
MF: C_7H_5BrClF
CAS #: 68220-26-8
MW: 223.47
MDL #: MFCD00040126
FP: 230
d: 1.6290

Score:69

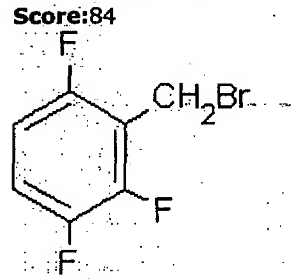


539090 96%

Zoom In

Name: **2,3,6-Trifluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1,3,4-trifluorobenzene**
MF: $C_7H_4BrF_3$
CAS #: 151412-02-1
MW: 225.01
MDL #: MFCD00061208
BP: 114 °C
FP: 195
d: 1.7180

Score:84

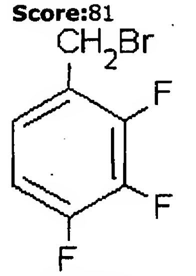


449407 97%

Zoom In

Name: **2,3,4-Trifluorobenzyl bromide**
IUPAC: **1-(bromomethyl)-2,3,4-trifluorobenzene**
MF: $C_7H_4BrF_3$
CAS #: 157911-55-2
MW: 225.01
MDL #: MFCD00061233
FP: 195
d: 1.71

Score:81

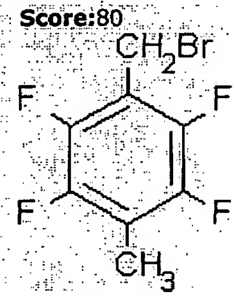


554685 97%

Zoom In

Name: **1-Bromomethyl-4-methyl-2,3,5,6-tetrafluorobenzene**
IUPAC: **1-(bromomethyl)-2,3,5,6-tetrafluoro-4-methylbenzene**
MF: $C_8H_5BrF_4$
CAS #: 92814-00-1
MW: 257.02
MDL #: MFCD03001155
FP: 199

Score:80

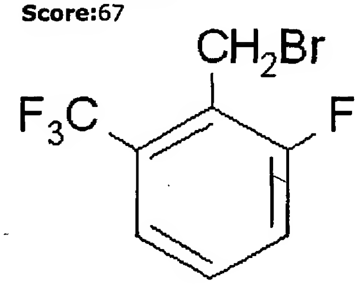


556491 97%

Zoom In

Name: **2-Fluoro-6-(trifluoromethyl)benzyl bromide**
IUPAC: **2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene**
MF: $C_8H_5BrF_4$
CAS #: 239087-08-2
MW: 257.02
MDL #: MFCD00082477
FP: 225

Score:67

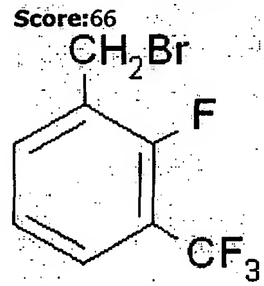


539627 98%

Zoom In

Name: **2-Fluoro-3-(trifluoromethyl)benzyl bromide**
IUPAC: **1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene**
MF: $C_8H_5BrF_4$
CAS #: 184970-25-0
MW: 257.02
MDL #: MFCD00061172

Score:66

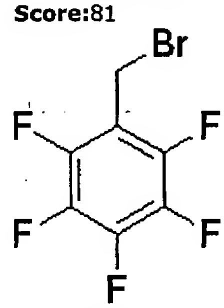


538094 97%

Zoom In

Name: **2,3,4,5,6-Pentafluorobenzyl bromide**
IUPAC: **1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene**
MF: $C_7H_2BrF_5$
CAS #: 1765-40-8
MW: 260.99
MDL #: MFCD00000299
BP: 174 - 175 °C
FP: 181
d: 1.7280

Score:81

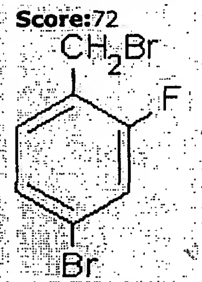


17910 puriss., ≥99.0% (GC)
101052 99%
33001 ampule of 5 g

Zoom In

Name: **4-Bromo-2-fluorobenzyl bromide**
IUPAC: **4-bromo-1-(bromomethyl)-2-fluorobenzene**
MF: $C_7H_5Br_2F$
CAS #: 76283-09-5
MW: 267.92
MDL #: MFCD00055467

Score:72

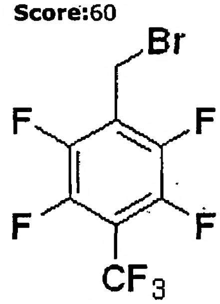


477559 98%

Zoom In

Name: **2,3,5,6-Tetrafluoro-4-(trifluoromethyl)benzyl bromide**
IUPAC: **1-(bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene**
MF: $C_8H_2BrF_7$
CAS #: 76437-40-6
MW: 310.99
MDL #: MFCD00191855
FP: 210
d: 1.8640

Score:60

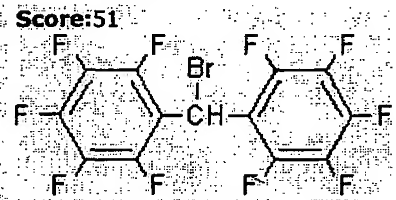


87285 purum, ≥97.0% (GC)
406406 98%

Zoom In

Name: **DECAFLUOROBENZHYDRYL BROMIDE**
IUPAC: **DECAFLUOROBENZHYDRYL BROMIDE**
MF: $C_{13}HBrF_{10}$
CAS #: 5736-4-9--2
MW: 427.04
MDL #: MFCD00017901

Score:51



Zoom In

Most disturbingly we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made. We can see that R_1 can be nothing but fluoro, trifluormethyl or chloro.

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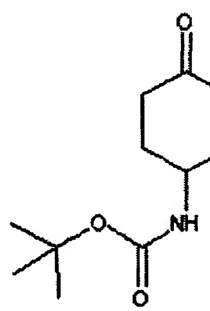
Search Type: SubStructure (2D)

Structure:

CLR NEW DEL D-R +/- UDO JME

C N O S F Cl Br I X



JME Editor courtesy of Peter Ertl, Novartis

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Search Results 0-0 of 0 in 1.0 sec. New Search

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Compound Properties | Structure | Add

No such cyclohexanones appear to be commercially available. While many phenols such as **8** are commercial, it would appear that the amide functionality (reverse as well) is required for activity, based on the fact that applicant has no examples of compounds that are not amides (in the ortho position) and the fact that Xue et. al. (supra) require the amide moiety for antagonism. To the examiners knowledge only one nosylglycidol, namely compound **9,** is commercial. Substituents should be limited to lower alkyl.

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required staring materials of formula **1**, **2**, **8,** and **9** are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the

less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730,734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *Inre Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). This is because it is not obvious from the disclosure of one species, what other species will work.

If such starting materials could be obtained compounds could be obtained it is very clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by

Grignards (Jie Jack Li *Name Reactions A Collection of Detailed Reaction Mechanisms* "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur (Knochel et. al. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.–4320). The "alkylhalo" compounds will undergo metal halogen exchange when in the presence of a Grignard (Knochel ibid.).

Another disturbing feature of what is before the examiner, is the fact that it appears that no assays were performed. These compounds may perform in this assay however this has not been asserted. There is no support in the specification for the use of these compounds as chemokine antagonists. While applicant states on pg. 40 "Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of M1P-1α chemokine." No evidence is given that these compounds actually were shown to have this activity. Given that similar compounds have the activity we can assume they have this activity (supra). The assumption that a chemokine receptor is involved may be incorrect, given that agonism at other GPCRs (δ-opiod receptors for instance), can lead to down regulation of chemokine receptors via heterodimers or higher oligomer complex formation (Chen et. al. *European Journal of Pharmacology* **2004**, *483*, 175-186.). The complete receptor profile of THP-1 cells is not known. Applicant may consider a binding assay as in Carroll et. al. WO 00/014086 cited by applicant ref. AG pg. 34:

plate counter.

The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ^{125}MIP-1α.

or Bondinell et. al. WO 01/64213 A1 pg. 23-25 cited by applicant ref. AH

<u>Biological Data:</u>

<u>CCR5 Receptor Binding Assay</u>

CHO cell membranes (0.25 x10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 or mCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 µM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists). Alternatively, this CCR5 receptor functional assay was performed on murine CCR5 (mCCR5) with a RANTES concentration of 2nM.

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 µM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 9 recite the limitation "solvate" in the claim. There is insufficient antecedent basis for this limitation in the claim.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, Ph.D. whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600

D.K.O.

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Sheet 1 of 1

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-503US1	Application No. 10/575,522
Information Disclosure Statement by Applicant (Use several sheets if necessary)	Applicant Nafizal Hossain	
(37 CFR §1.98(b))	Filing Date April 12, 2006	Group Art Unit 1625

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
DO	AA	EP 0004951	10/31/1979	Europe			Abstract	
DO	AB	EP 0004952	10/31/1979	Europe			Abstract	
	AC	~~EP 0417631~~	~~03/20/1991~~	~~Europe~~	Unreadable		Abstract	
DO	AD	EP 0722941	07/24/1996	Europe				
	AE	EP 1061076	12/20/2000	Europe				
	AF	WO 01/30780	05/03/2001	WIPO				
	AG	WO 02/102387	12/27/2002	WIPO				
	AH	WO 03/037271	05/08/2003	WIPO				
	AI	WO 2005/040167	05/06/2005	WIPO				
	AJ	WO 2005/049620	06/02/2005	WIPO				
	AK	WO 2005/054249	06/16/2005	WIPO				
	AL	WO 2005/061499	07/07/2005	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
DO	AM	Mehrotra et al., "Spirocyclic Nonpeptide Glycoprotein IIb-IIIa Antagonists. Part 3: Synthesis and SAR of Potent and Specific 2,8-Diazaspiro[4.5]decanes", *Bioorganic & Medicinal Chemistry Letters* 12:1103-1107 (2002)
DO	AN	Pujol et al., "Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines]", *Eur J Med Chem* 31:889-894 (1996)

Examiner Signature	Date Considered 5/16/07
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Substitute Disclosure Form (PTO-1449)

IAP15 Rec'd PCT/PTO 12 APR 2006

Sheet 1 of 1

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	Applicant Nafizal Hossain	
	Filing Date Herewith	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
DO	AA	4,010,201	03/01/1977	Lednicer			
DO	AB	4,263,317	04/21/1981	Martin et al.			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
DO	AC	WO 92/10096	06/25/1992	WIPO				
	~~AD~~	~~WO 96/36625~~	~~11/21/1996~~	~~WIPO~~	Abstract Only			
DO	AE	WO 98/25605	06/18/1998	WIPO				
DO	AF	WO 98/31364	07/23/1998	WIPO				
DO	AG	WO 00/14086	03/16/2000	WIPO				
DO	AH	WO 01/64213 A1	09/07/2001	WIPO				
DO	AI	WO 04/005295 A1	01/15/2004	WIPO				

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Notice of References Cited	Application/Control No. 10/575,522	Applicant(s)/Patent Under Reexamination HOSSAIN, NAFIZAL	
	Examiner David K. O'Dell, Ph.D.	Art Unit 1609	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2005/0245741 A1	11-2005	Hossain et al.	544/230
*	B	US-2006/0252751 A1	11-2006	Xue et al.	514/235.2
	C	US-			
	D	US-			
	E	US-			
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.
	V	Jie Jack Li Name Reactions A Collection of Detailed Reaction Mechanisms "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272.
	W	Knochel et. al. Angew. Chem. Int. Ed. 2003, 42, 4302 –4320.
	X	Chen et. al. European Journal of Pharmacology 2004, 483, 175-186.

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	U	Godessart, N. Chemokine Receptors: Attractive Targets for Drug Discovery, Annals of the New York Academy of Sciences 2005, 1051, 647-657.
	V	
	W	
	X	

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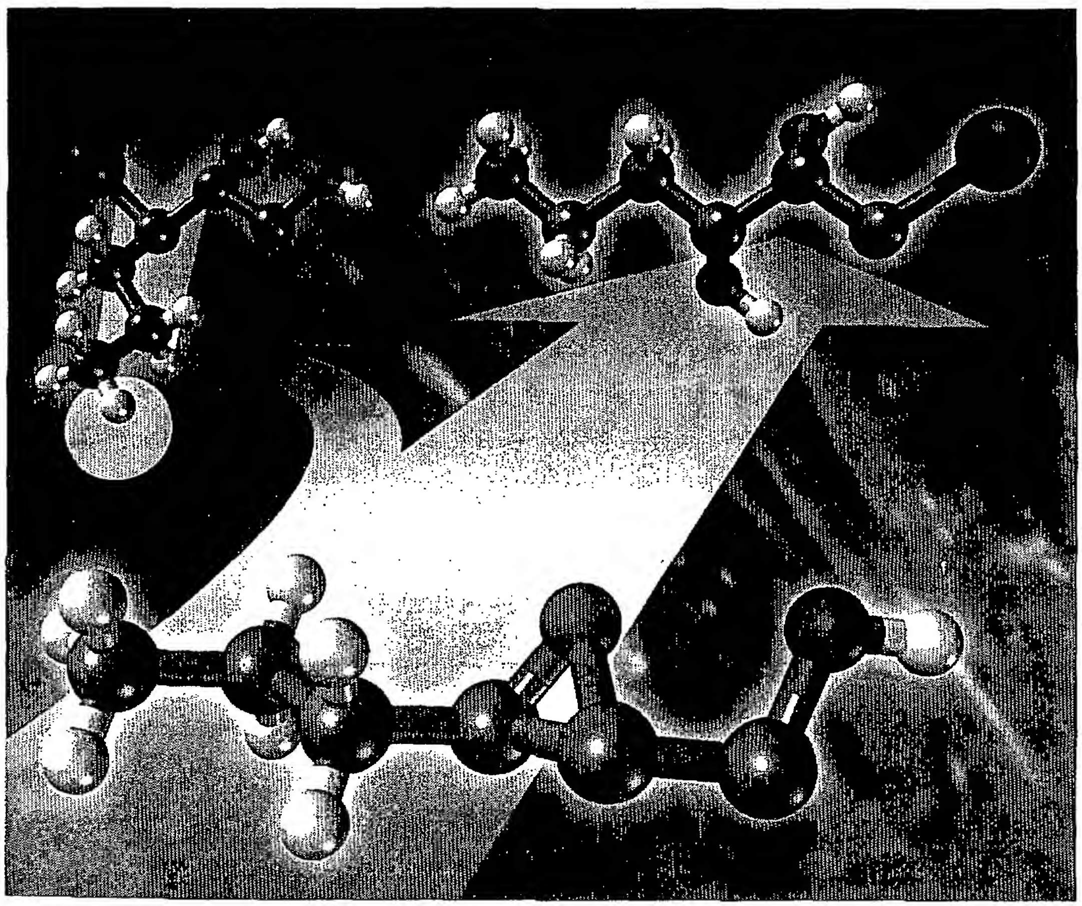
Side Reactions in Organic Synthesis

A Guide to Successful Synthesis Design



Florencio Zaragoza Dörwald

Side Reactions in Organic Synthesis

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Preface

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

This book attempts to highlight the competing processes and limitations of some of the most common and important reactions used in organic synthesis. Awareness of these limitations and problem areas is important for the design of syntheses, and might also aid elucidation of the structure of unexpected products. Two chapters of this book cover the structure–reactivity relationship of organic compounds, and should also aid the design of better syntheses.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious). Nevertheless, I have ventured to describe some reactions as difficult or impossible. A talented chemist might, however, succeed in performing such reactions anyway, for what I congratulate him in advance. The aim of this book is not to stop the reader from doing bold experiments, but to help him recognize his experiment as bold, to draw his attention to potential problems, and to inspire, challenge, and motivate.

Side Reactions in Organic Synthesis. Florencio Zaragoza Dörwald

ISBN: 3-527-31021-5

Jie Jack Li

Name Reactions

A Collection of Detailed Reaction Mechanisms

Third Expanded Edition

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Dedicated to

Professor E. J. Corey

Foreword

I don't have my name on anything that I don't really do.
–Heidi Klum

Can the organic chemists associated with so-called "Named Reactions" make the same claim as supermodel Heidi Klum? Many scholars of chemistry do not hesitate to point out that the names associated with "name reactions" are often not the actual inventors. For instance, the Arndt-Eistert reaction has nothing to do with either Arndt or Eistert, Pummerer did not discover the "Pummerer" rearrangement, and even the famous Birch reduction owes its initial discovery to someone named Charles Wooster (first reported in a DuPont patent). The list goes on and on...

But does that mean we should ignore, boycott, or outlaw "named reactions"? Absolutely not. The above examples are merely exceptions to the rule. In fact, the chemists associated with name reactions are typically the original discoverers, contribute greatly to its general use, and/or are the first to popularize the transformation. Regardless of the controversial history underlying certain named reactions, it is the students of organic chemistry who benefit the most from the cataloging of reactions by name. Indeed, it is with **education** in mind that Dr. Jack Li has masterfully brought the chemical community the latest edition of *Name Reactions*.

It is clear why this beautiful treatise has rapidly become a bestseller within the chemical community. The quintessence of hundreds of named reactions is encapsulated in a concise format that is ideal for students and seasoned chemists alike. Detailed mechanistic and occasionally even historical details are given for hundreds of reactions along with key references. This "must-have" book will undoubtedly find a place on the bookshelves of all serious practitioners and students of the art and science of synthesis.

Phil S. Baran
La Jolla, March 2006

Preface

Confucius said: *"Reviewing old knowledge while learning new old knowledge, is that not, after all, a pleasure?"* Indeed, name reactions are not only the fruit of pioneering organic chemists, but also our contemporaries whose combined discoveries have resulted in organic chemistry today. Since publication of this book, Barry Sharpless and Ryoji Noyori, whose name reactions have been included since the first edition, went on to win the Nobel Prizes in 2001. Recently, Richard Schrock, Robert Grubbs, and Yves Chauvin shared the 2005 Nobel Prize in chemistry for their contributions to metathesis, a name reaction that has been also included since the first edition. Therefore, I intend to keep up with the new developments in the field of organic chemistry while retaining the collection of name reactions that have withheld test of time.

The third edition contains major improvements over the previous two editions. I have updated references. Each reaction is now supplemented with two to three representative examples in synthesis to showcase its synthetic utility. As Emil Fischer stated: *"Science is not an abstraction; but as a product of human endeavor it is inseparably bound up in its development with the personalities and fortunes of those who dedicate themselves to it."* To that end, I added biographical sketches for most of the chemists who discovered or developed those name reactions. Furthemore, I have significantly beefed up the subject index to help the reader navigate the book more easily.

In preparing this manuscript, I have incurred many debts of gratitude to Prof. Reto Mueller of Switzerland, Prof. Robin Ferrier of New Zealand, and Prof. James M. Cook of the University of Wisconsin, Milwaukee; Dr. Yike Ni of California Institute of Technology, and Dr. Shengping Zheng of Columbia University for invaluable suggestions. I also wish to thank Dr. Gilles Chambournier, Prof. Phil S. Baran of Scripps Research Institute and his students, Narendra Ambhaikar, Ben Hafensteiner, Carlos Guerrero, and Dan O'Malley, Prof. Brian M. Stoltz of California Institute of Technology and his students, Kevin Allan, Daniel Caspi, David Ebner, Andrew Harned, Shyam Krishnan, Michael Krout, Qi Charles Liu, Sandy Ma, Justin Mohr, John Phillips, Jennifer Roizen, Brinton Seashore-Ludlow, Nathaniel Sherden, Jennifer Stockdill, and Carolyn Woodroofe for proofreading the final draft of the manuscript. Their knowledge and time have tremendously enhanced the quality of this book. Any remaining errors are, of course, solely my own responsibility.

I welcome your critique.

Jack Li
Ann Arbor, Michigan, March 2006

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Abbreviations and Acronyms

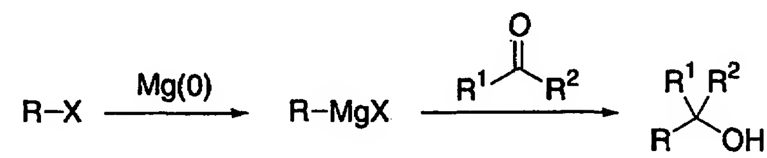
	polymer support
A	adenosine
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alpine-borane®	*B*-isopinocampheyl-9-borabicyclo[3.3.1]-nonane
Ar	aryl
B:	generic base
9-BBN	9-borabicyclo[3.3.1]nonane
[bimim]Cl•2AlCl$_3$	1-butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
t-Bu	*tert*-butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
m-CPBA	*m*-chloroperoxybenzoic acid
CuTC	copper thiophene-2-carboxylate
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Δ	solvent heated under reflux
(DHQ)$_2$-PHAL	1,4-bis(9-*O*-dihydroquinine)-phthalazine
(DHQD)$_2$-PHAL	1,4-bis(9-*O*-dihydroquinidine)-phthalazine
DIAD	diisopropyl azodidicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane

DTBAD	di-*tert*-butylazodicarbonate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E1	unimolecular elimination
E2	bimolecular elimination
E1cB	2-step, base-induced β-elimination *via* carbanion
EAN	ethylammonium nitrate
EDDA	ethylenediamine diacetate
ee	enantiomeric excess
Ei	two groups leave at about the same time and bond to each other as they are doing so.
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMTTA	1,1,4,7,10,10-hexamethyltriethylenetetramine
Imd	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	metal
Mes	mesityl
Ms	methanesulfonyl
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
Nos	nosylate (4-nitrobenzenesulfonyl)
Nu	nucleophile
N-PSP	*N*-phenylselenophthalimide
N-PSS	*N*-phenylselenosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	para-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
$PyPh_2P$	diphenyl 2-pyridylphosphine
Pyr	pyridine
Red-Al	sodium bis(methoxy-ethoxy)aluminum hydride (SMEAH)
Salen	*N,N′*-disalicylidene-ethylenediamine
SET	single electron transfer
SM	starting material

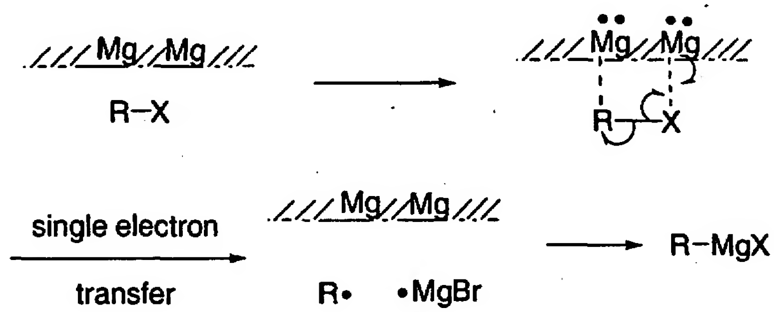
SMEAH	sodium bis(methoxy-ethoxy)aluminum hydride (Red-Al)
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic substitution on an aromatic ring
TBABB	tetra-*n*-butylammonium bibenzoate
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEOC	trimethysilylethoxycarbonyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMG	tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
TosMIC	(*p*-tolylsulfonyl)methyl isocyanide
Ts	tosyl
TsO	tosylate
UHP	urea-hydrogen peroxide

Grignard reaction

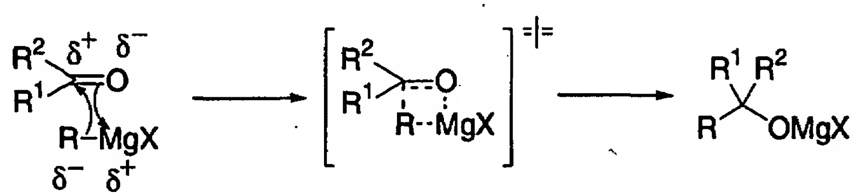
Addition of organomagnesium compounds (Grignard reagents), generated from organohalides and magnesium metal, to electrophiles.



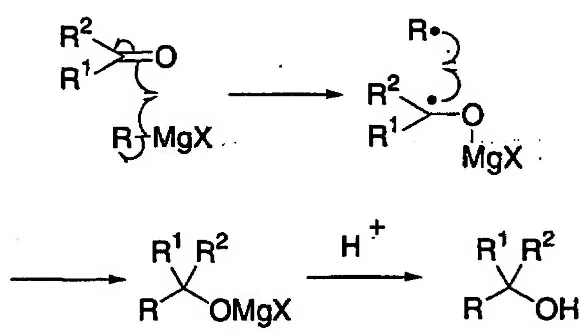
Formation of the Grignard reagent:



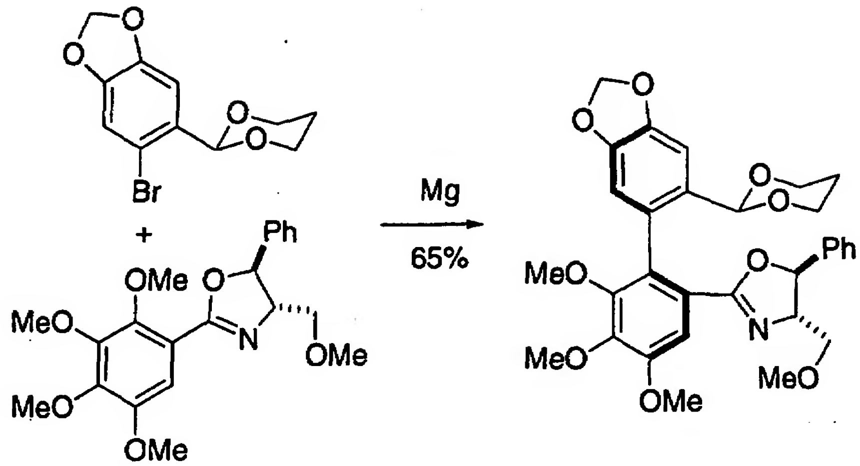
Grignard reaction, ionic mechanism:



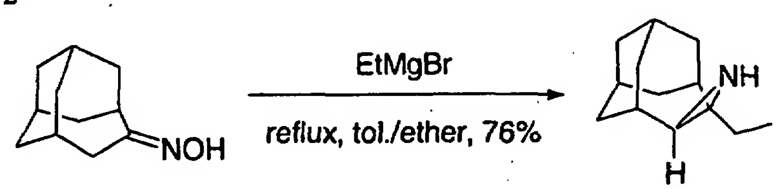
Radical mechanism,



Example 1[6]



Example 2[4]



This reaction is known as the **Hoch–Campbell aziridine synthesis**, which entails treatment of ketoximes with excess Grignard reagents and subsequent hydrolysis of the organometallic complex to produce aziridines.

References

1. Grignard, V. *C. R. Acad. Sci.* **1900**, *130*, 1322. Victor Grignard (France, 1871–1935) won the Nobel Prize in Chemistry in 1912 for his discovery of the Grignard reagent.
2. Ashby, E. C.; Laemmle, J. T.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272. (Review).
3. Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. (Review).
4. Sasaki, T.; Eguchi, S.; Hattori, S. *Heterocycles* **1978**, *11*, 235.
5. Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M. L. *Tetrahedron* **1980**, *36*, 3403.
6. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.
7. *Grignard Reagents* Richey, H. G., Jr., Ed.; Wiley: New York, 2000. (Book).
8. Holm, T.; Crossland, I. In *Grignard Reagents* Richey, H. G., Jr., Ed.; Wiley: New York, 2000, Chapter 1, pp 1–26. (Review).
9. Toda, N.; Ori, M.; Takami, K.; Tago, K.; Kogen, H. *Org. Lett.* **2003**, *5*, 269.
10. Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081–2091. (Review).
11. Graden, H.; Kann, N. *Cur. Org. Chem.* **2005**, *9*, 733–763. (Review).

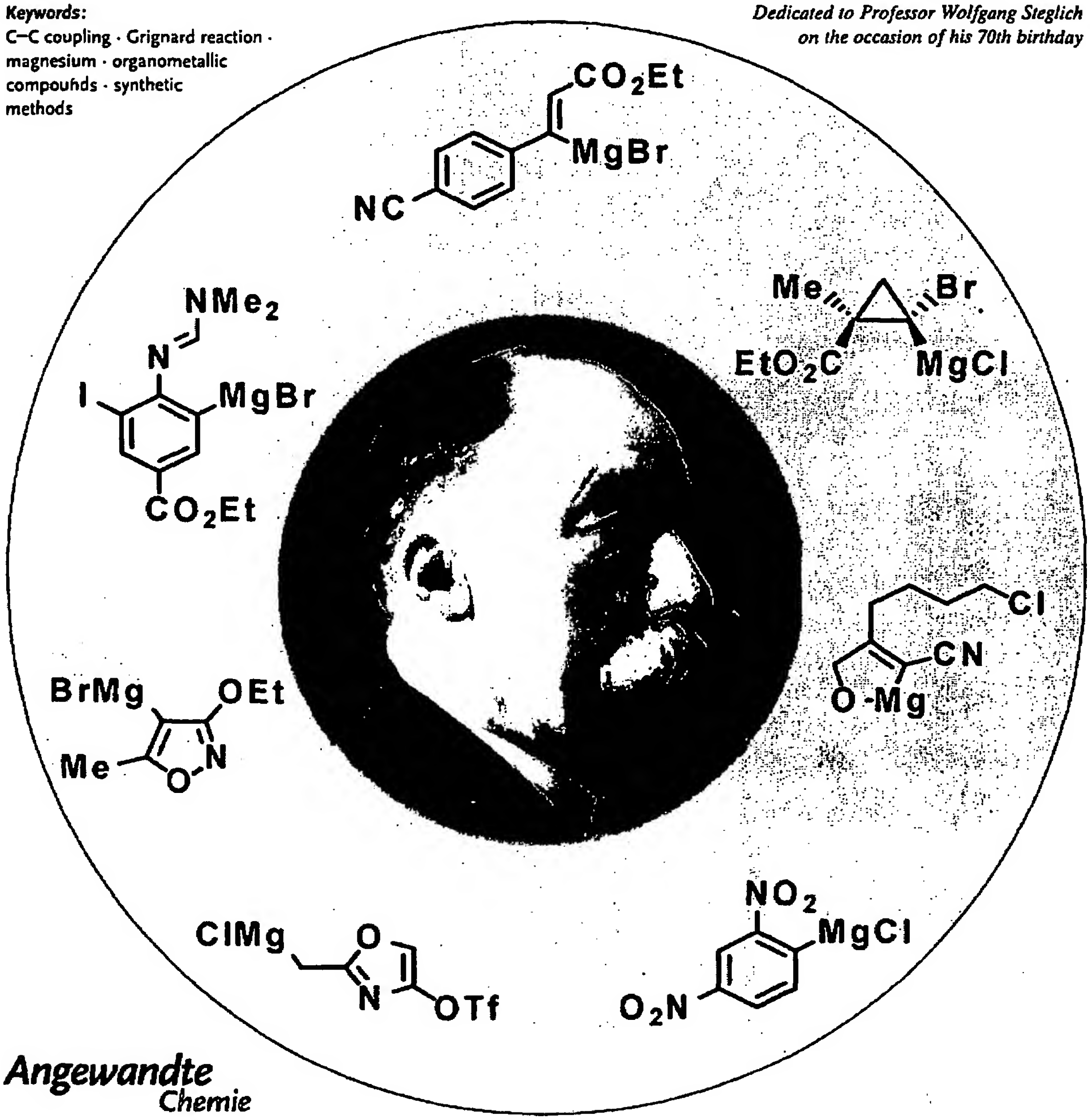
Grignard Reagents in Synthesis

Highly Functionalized Organomagnesium Reagents Prepared through Halogen–Metal Exchange

Paul Knochel, Wolfgang Dohle, Nina Gommermann, Florian F. Kneisel, Felix Kopp, Tobias Korn, Ioannis Sapountzis, and Viet Anh Vu*

Keywords:
C–C coupling · Grignard reaction · magnesium · organometallic compounds · synthetic methods

Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday



Angewandte Chemie

Organomagnesium reagents occupy a central position in synthetic organic and organometallic chemistry. Recently, the halogen–magnesium exchange has considerably extended the range of functionalized Grignard reagents available for synthetic purposes. Functional groups such as esters, nitriles, iodides, imines, or even nitro groups can be present in a wide range of aromatic and heterocyclic organomagnesium reagents. Also various highly functionalized alkenyl magnesium species can be prepared. These recent developments as well as new applications of organomagnesium reagents in cross-coupling reactions and amination reactions will be covered in this Review.

From the Contents

1. Introduction

Access to functionalized organometallic compounds has considerably increased the scope of these nucleophilic reagents in organic synthesis.[1] The presence of sensitive functional groups makes their preparation more complicated, and a number of conventional methods are often not appropriate or not general. The direct oxidative addition of activated metals to organic halides,[2,3] carbometallation,[4] hydrometallation,[5] or selective deprotonation[6] have been used successfully, but generally have limited functional-group tolerance. The halogen–lithium exchange reaction discovered by Wittig et al.[7] and Gilman and co-workers[8] allows the preparation of a broad range of organolithium compounds,[9] although the functional-group tolerance is modest. In contrast, the halogen–magnesium exchange has been found to be the method of choice for preparing new functionalized organomagnesium reagents of considerable synthetic utility.

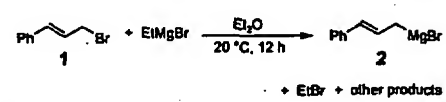
Herein, we wish to give an overview of the dramatic advances in the synthesis of functionalized Grignard reagents and to demonstrate its broad applicability. Organomagnesium reagents were first prepared over 100 years ago by Grignard and still occupy a central place in organic chemistry. Organomagnesium compounds have an excellent reactivity towards a wide range of electrophiles and readily undergo transmetallation to provide a variety of organometallic reagents,[10] particularly organocopper reagents, which react especially well with soft electrophiles and display excellent chemoselectivity.[11]

2. The Halogen–Magnesium Exchange

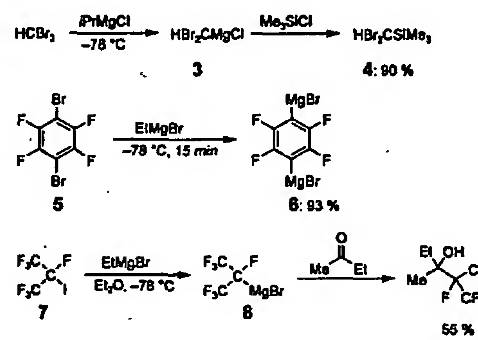
2.1. Early Work

Whereas the direct reaction of magnesium metal with organic halides is the most common method used to prepare organomagnesium compounds, the first example of a bromine–magnesium exchange reaction was briefly reported in 1931 by Prévost.[12] Thus, the reaction of cinnamyl bromide (**1**) with EtMgBr furnished cinnamylmagnesium bromide (**2**), albeit in a moderate yield (Scheme 1).[12]

The halogen–magnesium exchange reaction was the first general approach to magnesium carbenoids.[13] Villiéras and co-workers found that the reaction of *i*PrMgCl with $CHBr_3$ at −78 °C furnished the corresponding magnesium carbenoid **3**, which could be trapped with electrophiles to provide products of type **4** (Scheme 2). This pioneering work opened the way to the systematic study of magnesium carbenoids[14] and demonstrated that the halogen–magnesium exchange rate is enhanced by the presence of electronegative substituents. This behavior was confirmed a few years later by the work of Tamborski and Moore,[15] who found that 1,4-dibromo-2,3,5,6-tetrafluorobenzene (**5**) is readily converted into the corresponding 1,4-dimagnesium species **6** with EtMgBr (Scheme 2). Similarly, Furukawa et al. showed that



Scheme 1. First example of a halogen–magnesium exchange.



Scheme 2. Bromine–magnesium exchange of polyhalogenated compounds.

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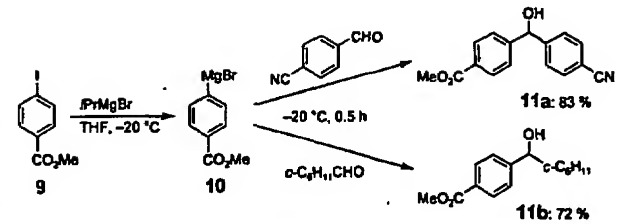
2-iodopyridine leads to the corresponding Grignard reagent within 30 min by the reaction with EtMgBr at 25°C.[16] Interestingly, perfluoroalkyl iodides such as 7 undergo iodine–magnesium exchange at −78°C to give the perfluorinated Grignard reagent 8, which reacts well with carbonyl compounds (Scheme 2).[17]

These early results demonstrate the synthetic potential of the halogen–magnesium exchange reaction.[18] The reactivity of organomagnesium reagents is strongly dependent on the reaction temperature: Only reactive electrophiles such as aldehydes and most ketones react rapidly at temperatures below 0°C. Thus, performing the halogen–magnesium exchange at temperatures below 0°C has the potential for the preparation of magnesium organometallic reagents that bear reactive functional groups. Access to functionalized Grignard reagents will considerably expand the current scope of organomagnesium reagents in organic synthesis with the added benefit inherent to bifunctional reagents.

2.2. Functionalized Aryl Magnesium Reagents

Functionalized aryl iodides react readily with iPrMgBr or iPrMgCl in THF below 0°C, leading to a range of functionalized aryl magnesium iodides.[19] Sensitive carbonyl group derivatives such as nitriles, esters, or amides are tolerated. Typically, treatment of methyl 4-iodobenzoate (9) with iPrMgBr in THF at −20°C for 1 h produces the functionalized Grignard reagent 10, which is stable for several hours below −10°C, but reacts smoothly with aldehydes at −20°C leading to the expected alcohols 11a,b in 72 and 83% yields, respectively (Scheme 3).[20]



Scheme 3. The reaction of ester-containing aryl magnesium reagents with aldehydes.

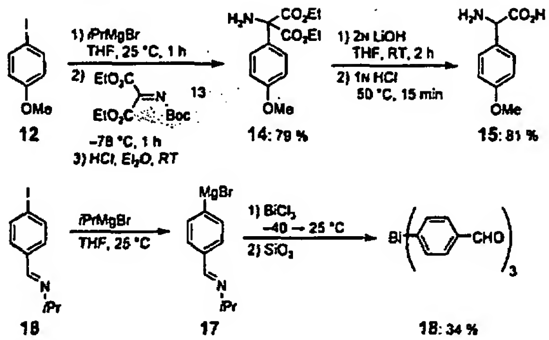
Aromatic iodides such as 12 that bear electron-donating groups undergo iodine–magnesium exchange only at higher temperatures (25°C).[19,21] The addition of the resulting aryl magnesium species to diethyl N-Boc-iminomalonate (13)[22] furnishes the adduct 14 in 79% yield. Saponification followed by decarboxylation provides the α-amino acid 15 in 81% yield (Scheme 4).[21] Whereas aldehyde-containing aryl iodides preferentially react with the aldehyde group during attempted iodine–magnesium exchange, the corresponding imine (16) undergoes a smooth exchange reaction, leading to the Grignard reagent 17. The imino group of 13 is considerably more reactive than that of 16, which explains the compatibility of the later under the conditions used for forming the magnesium reagent 17. The addition of $BiCl_3$ followed by purification by silica-gel column chromatography provides the resulting functionalized triarylbismuthane 18 (Scheme 4).[23]

Paul Knochel was born in 1955 in Strasbourg (France). He completed his undergraduate studies at the University of Strasbourg and his PhD at the ETH Zürich with Prof. D. Seebach (1982). He spent 4 years with Prof. J.-F. Normant (Paris) and 1 year with Prof. M. F. Semmelhack (Princeton) as a postdoctoral researcher. After professorships at the University of Michigan (Ann Arbor) and the Philipps-Universität (Marburg), he moved to the Ludwig-Maximilians-Universität (Munich) in 1999. His research interests include the development of new synthetic methods with organometallic reagents, new asymmetric catalysts, and natural product synthesis.

Nina Gommermann was born in Kassel (Germany) in 1978. After undergraduate studies at the Philipps-Universität in Marburg and at the Ludwig-Maximilians-Universität in Munich (1997–2002), she joined Prof. Knochel in 2001 for her diploma thesis and started her PhD in the same group in 2002. Her work is concentrated on enantioselective synthesis.

Wolfgang Dohle was born in Winterberg (Germany) in 1970. He completed his undergraduate studies at the Philipps-Universität in Marburg (1992–99). He joined Prof. Knochel in 1998 for his diploma thesis, and moved with him to the Ludwig-Maximilians-Universität in Munich, where he finished his PhD at the end of 2002. His work was focused on functionalized Grignard reagents for the synthesis of heterocycles and transition-metal-catalyzed cross-coupling reactions.

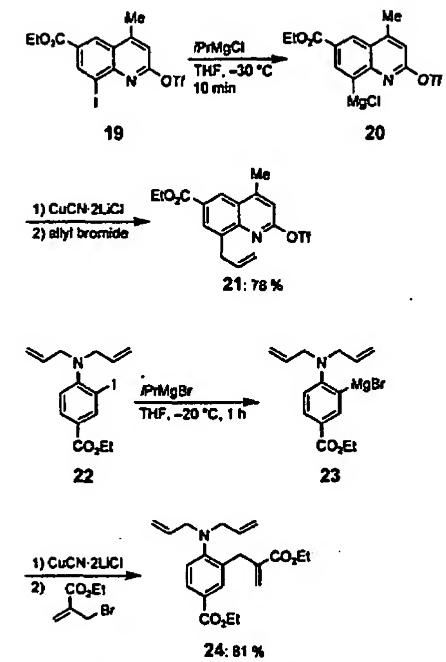
Florian Felix Kneisel was born 1975 in Darmstadt (Germany). He studied chemistry at the Philipps-University of Marburg (Germany) and at the University of Cambridge (UK). He completed his diploma thesis (2000) on macromolecular chemistry under the supervision of Prof. W. Heitz (Philipps-Universität, Marburg). In the same year he began his PhD with Prof. Dr. P. Knochel, dealing with intramolecular cross-coupling reactions, allylic substitutions, and new syntheses of organometallic reagents.



Scheme 4. Reactivity and compatibility of imine groups within an aryl magnesium reagent. Boc = *tert*-butoxycarbonyl.

A wide range of basic nitrogen functionalities are compatible with the iodine–magnesium exchange. Thus, the functionalized iodoquinoline **19** is converted at −30 °C in 10 min into the corresponding magnesium reagent **20**. Transmetallation with CuCN·2 LiCl[24] and the reaction with allyl bromide furnishes the allylated quinoline **21** in 78% yield (Scheme 5).[25] Similarly, the diallylaniline **22** is allylated via the intermediate Grignard reagent **23**, leading to the functionalized aniline derivative **24** in 81% yield (Scheme 5).[20]

Labile amidine[26] and imine protecting groups are stable to magnesium–halogen exchange and are convenient derivatives for introducing primary amine functions in a molecule. Thus, the diiodoamidine **25** is converted within 5 min at −20 °C into the aryl magnesium species **26**. Remarkably, only one iodine–magnesium exchange reaction takes place. After the first I/Mg exchange the electron density of the aromatic



Scheme 5. Aryl magnesium compounds containing nitrogen functional groups. Tf = trifluoromethanesulfonyl.

ring increases which hampers a second exchange. Transmetallation of **26** with CuCN·2 LiCl provides the aryl copper derivative **27**, which readily undergoes an addition–elimination reaction with various β-iodocarbonyl compounds such as

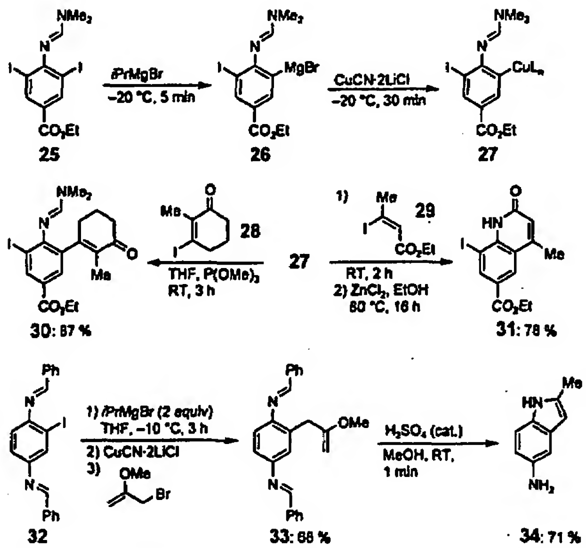
Felix Kopp was born in 1978 in Augsburg (Germany). He studied chemistry at the Ludwig-Maximilians-Universität in Munich and joined Prof. Knochel for his diploma thesis on new amination reactions using functionalized Grignard reagents. He is now working on his PhD in the same group.

Ioannis Sapountzis was born in Pforzheim (Germany) in 1975. After his undergraduate studies at the Ludwig-Maximilians-Universität in Munich (1996–2001), he joined Prof. Knochel for his diploma thesis and started his PhD thesis in the same group in 2001. His work is focused on reactions of nitroarenes and related nitrogen derivatives with organomagnesium reagents as well as the generation of functionalized alkenyl Grignard reagents.

Tobias Korn, born in 1976 in Dachau (Germany), completed his undergraduate studies at the Ludwig-Maximilians Universität in Munich (1997–2002). After his diploma thesis with Prof. Gerhard Hilt, he started his PhD in December 2002 under the supervision of Prof. Knochel. His work is focused on transition-metal-catalyzed cross-coupling reactions.

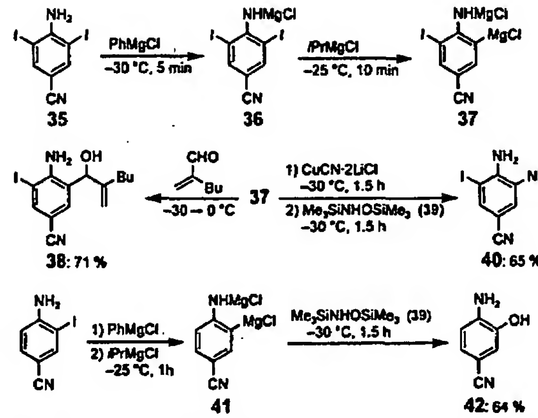
Viet Anh Vu was born in 1974 in Hanoi (Vietnam). He completed his undergraduate studies at the Ho chi Minh University of Medicine and Pharmacy (Vietnam, 1991–96). After his MSc at the Vrije Universiteit Brussel (Belgium, 1998–2000), he started his PhD with Prof. Knochel in 2000. His work is focused on the preparation of new functionalized organomagnesium compounds.

28 or 29 to furnish either directly the corresponding α,β-unsaturated carbonyl compound 30[27] in 87% yield, or, after the removal of the amidine function and cyclization, the heterocycle 31[28] in 78% yield (Scheme 6). Likewise, the diimine 32 undergoes an iodine–magnesium exchange with *i*PrMgBr (2 equiv) at −10°C in 3 h. Transmetallation to the copper derivative by treatment with CuCN·2 LiCl[24] and allylation with 2-methoxyallyl bromide gives the diimine 33 in 68% yield. Deprotection of the two amino functions, and of the vinylic ether, with concentrated H_2SO_4 furnishes the indole 34 in 71% yield.[29]



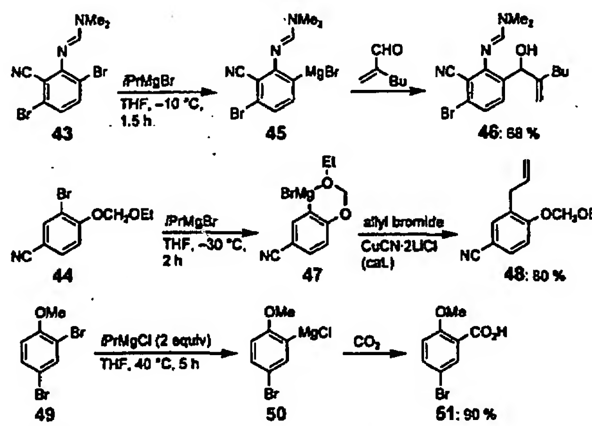
Scheme 6. Preparation of iminoaryl magnesium reagents for the synthesis of heterocycles. $L_n = MgX_2$, LiX.

Unprotected functionalized iodoanilines can also be used to prepare Grignard reagents. The successive addition of PhMgCl (−30°C, 10 min) and *i*PrMgCl (−25°C, 10 min) to the diiodoaniline 35 gives, via the magnesium amide 36, the dimagnesium derivative 37, which reacts in satisfactory yields with an aldehyde to give the polyfunctionalized benzylic alcohol 38 (Scheme 7).[30] Interestingly, after transmetallation with CuCN·2 LiCl,[24] the resulting copper reagent reacts with *N,O*-bis(trimethylsilyl)hydroxylamine (39) to afford the diamine 40 in 65% yield. The direct reaction of 39[31] with an aryl magnesium reagent such as 41 provides the corresponding 2-hydroxyaniline 42 in 64% yield (Scheme 7).[30] Collectively, these I/Mg exchanges demonstrate a versatile preparation of a range of aminated aryl magnesium reagents that is not complicated by the deactivation of magnesium metal in the more standard preparation of aryl magnesium species from aryl halides and magnesium turnings.



Scheme 7. Reactions of unprotected aminoaryl magnesium reagents.

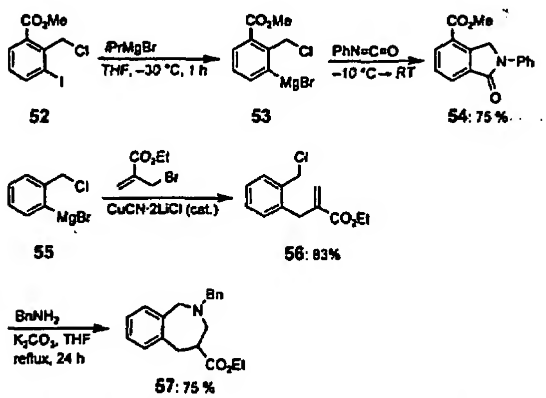
The Br/Mg exchange reaction, although slower than I/Mg exchange, is sufficiently fast below 0°C for preparing functionalized aryl magnesium bromides that bear electron-withdrawing groups. Therefore, Br/Mg exchange is suitable for the preparation of Grignard reagents that bear sensitive functional groups. The exchange rate depends strongly on the electron density of the aromatic ring. Thus, whereas bromopentafluorobenzene undergoes complete Br/Mg exchange at −78°C within 30 min, 1-bromo-2,4,5-trifluorobenzene requires 1 h at −10°C for a full conversion into the corresponding magnesium reagent.[32] Polyfunctionalized aromatic bromides such as 43[27] and 44[33] (Scheme 8) that bear a chelating group at the *ortho* position, rapidly undergo Br/Mg exchange. The chelating group complexes *i*PrMgBr prior to the Br/Mg exchange, which facilitates this exchange through an intramolecular reaction. Thus, the dibromide 43 undergoes a chemoselective Br/Mg exchange, leading only to the reagent 45, in which the MgBr group is *ortho* to the amidine functionality. After the addition to 2-butylacrolein, the expected alcohol 46 is formed in 68% yield.[27] An oxygen chelating functional group such as an ethoxymethyl group in the aryl bromide 44 enhances the Br/Mg exchange rate,



Scheme 8. Br/Mg exchange of functionalized aromatic bromides.

allowing the preparation of the magnesium derivative **47** at −30 °C within 2 h. In the presence of a catalytic amount of CuCN·2 LiCl (10 mol%), **47** undergoes an allylation with allyl bromide to provide the aromatic nitrile **48** in 80% yield.[32] Less effective chelating groups such as a methoxy function require higher reaction temperatures. For example, 2,4-dibromoanisole (**49**) is converted into the corresponding aryl magnesium compound **50** by treatment with *i*PrMgCl (2 equiv) in THF at 40 °C for 5 h. After the addition of CO_2, the corresponding carboxylic acid **51** is obtained in 90% yield (Scheme 8).[18d]

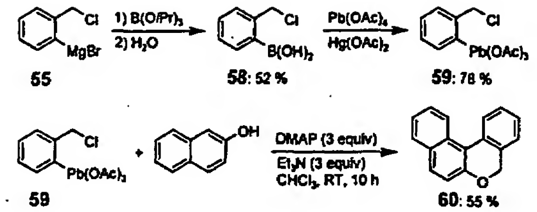
The incorporation of electrophilic functional groups *ortho* to the carbon–magnesium bond allows two sequential alkylations, leading to ring closure (Scheme 9). Treatment of the



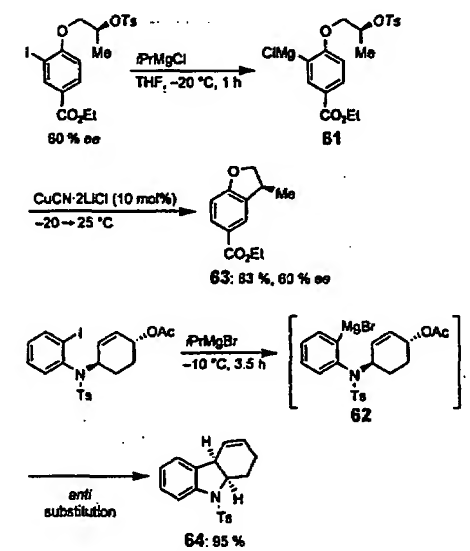
Scheme 9. Reaction of chloromethyl-substituted aryl magnesium species.

benzylic chloride **52** with *i*PrMgBr in THF (−30 °C, 1 h) furnishes the corresponding Grignard reagent **53**, which reacts at −10 °C with phenyl isocyanate to give the functionalized *N*-phenylphthalimide derivative **54** in 75% yield.[33] The reaction of the related aryl magnesium species **55** with ethyl 2-(bromomethyl)acrylate[34] furnishes the polyfunctionalized product **56** in 83% yield. Subsequent treatment of **56** with benzylamine in the presence of K_2CO_3 in refluxing THF provides the benzoazepine **57** in 75% yield.[33]

In strong contrast to the corresponding lithium reagent, which is stable only at −100 °C,[35] the magnesium species **55** is stable for several hours at −30 °C. The reagent **55** was recently transmetallated to the boronic acid **58** by the reaction with $B(OiPr)_3$ and subsequent hydrolysis. The boronic acid **58** reacted with $Pb(OAc)_4$ to give the lead derivative **59**, allowing an expeditious preparation of **60** in 55% yield (Scheme 10).[35] Complementary cyclizations can be achieved with functionalized aryl magnesium reagents that bear a more remote leaving group such as a tosylate (e.g. **61**) or an allylic acetate (e.g. **62**). In both cases, a stereoselective substitution reaction was observed (Scheme 11).[36] The S_N2 ring closure of **61** is catalyzed by CuCN·2 LiCl[24] and proceeds with complete inversion of configuration; **63** was obtained without eroding the original 60% *ee*. An *anti* S_N2' substitution is observed with



Scheme 10. Preparation and reaction of chloromethyl-substituted aryl organometallic compounds. DMAP = 4-dimethylaminopyridine.

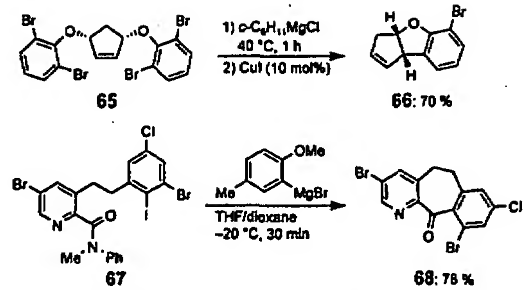


Scheme 11. Stereoselective ring closure of aryl magnesium intermediates. Ts = *p*-toluenesulfonyl.

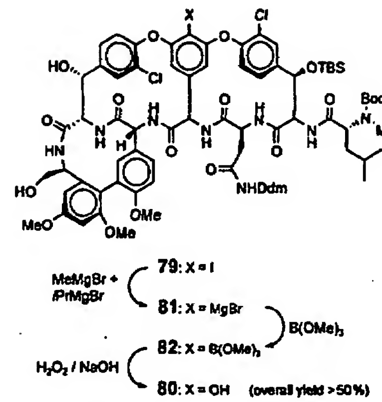
62, providing the *cis*-tetrahydrocarbazole **64** in quantitative yield. In this case, the Grignard reagent undergoes ring closure in the absence of a catalyst.[36]

*i*PrMgCl is the magnesium reagent of choice for the halogen–magnesium exchange. However, in some cases, the use of more (or less) reactive organomagnesium compounds is advantageous. Thus, a Br/Mg exchange reaction between cyclohexylmagnesium chloride and allylic tetrabromo ether **65** at 40 °C with a subsequent copper-catalyzed *syn* S_N2' substitution reaction furnishes the benzofuran derivative **66** in 70% yield.[18d] In the synthesis of a potent farnesyl protein transferase inhibitor, the polyfunctionalized amide **67** needed to be converted into the tricyclic product **68**. This was achieved through an iodine–magnesium exchange reaction with 2-methoxy 5-methyl-phenylmagnesium bromide in a THF:dioxane mixture. The reaction was complete within 30 min at −20 °C and led to the cyclized product **68** in 78% yield (Scheme 12).[37]

Functionalized aryl magnesium compounds allow direct aminomethylation reactions with various carbonyl compounds. Thus, the Grignard reagent **69** adds to the iminium trifluoroacetate **70** in THF/CH_2Cl_2 at −60 °C within 30 min, providing the diallylamine **71** in 76% yield. Deallylation by

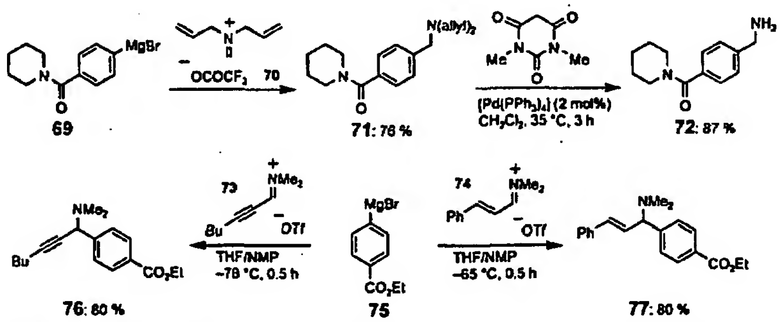


Scheme 12. Cyclizations mediated by halogen–magnesium exchange.



Scheme 15. Formation of a functionalized aryl magnesium compound during the synthesis of vancomycin. Ddm = 4,4'-dimethoxyphenylmethyl, TBS = *tert*-butyldimethylsilyl.

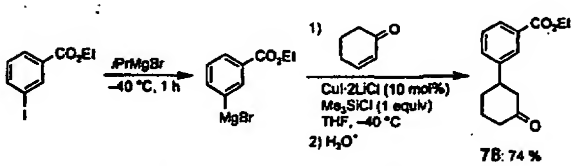
the method of Guibé and co-workers[38] provides the aminomethylation product **72** in 87% yield.[39] Various unsaturated iminium salts such as **73** and **74** react with functionalized aryl magnesium halides, for example, **75**, to furnish the expected benzylic amines **76** and **77**, respectively, in yields of 80% (Scheme 13).[40]



Scheme 13. Reaction of functionalized aryl magnesium compounds with iminium salts. NMP = *N*-methylpyrrolidinone.

In the presence of catalytic amounts of CuI·2 LiCl and Me_3SiCl (1 equiv),[41] functionalized aryl magnesium compounds can be added to various cyclic and acyclic enones, providing Michael-addition products of type **78** (Scheme 14).[42]

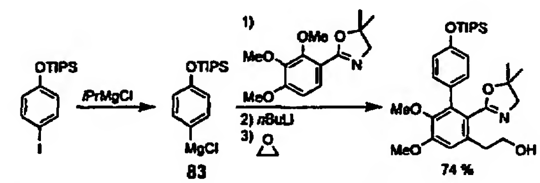
The iodine–magnesium exchange can be applied to the synthesis of complex natural products. A selective conversion by Nicolaou and co-workers of the aryl iodide **79** (X = I) into the corresponding phenol **80** (X = OH) was needed in the final steps of the synthesis of the antibiotic vancomycin (Scheme 15).[43] The aryl iodide **79** was converted into the corresponding Grignard reagent **81** by the reaction with a



Scheme 14. Cu^I^-catalyzed addition of functionalized aryl magnesium compounds to enones.

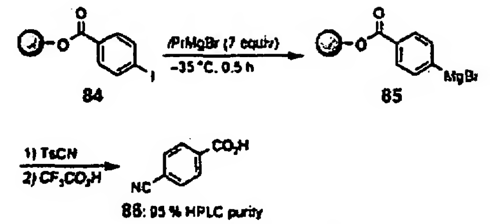
combination of MeMgBr and *i*PrMgBr (excess) at −40°C followed by the addition of $B(OMe)_3$, leading to the boronic ester **82**. The reaction of **82** with an alkaline solution of H_2O_2 furnished the desired phenol **80** in approximately 50% overall yield.

Functionalized aryl magnesium chlorides such as **83**, prepared by I/Mg exchange, readily undergo addition reactions to aryl oxazolines. The addition–elimination of **83** to a trimethoxyaryl oxazoline followed by *ortho* lithiation and substitution with ethylene oxide led to a polyfunctionalized aromatic intermediate that was required in the synthesis of an alkaloid (Scheme 16).[44]



Scheme 16. Formation of a functionalized aryl magnesium compound in the course of the synthesis of an alkaloid. TIPS = triisopropylsilyl.

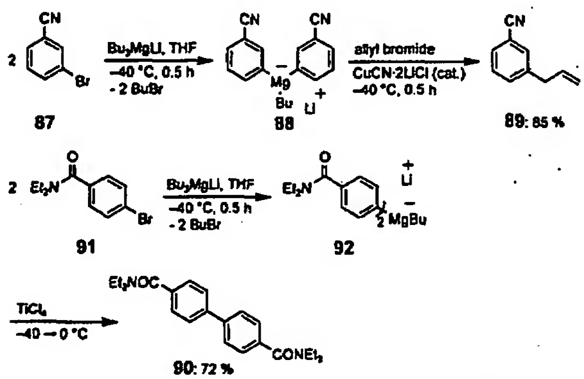
Polyfunctionalized organomagnesium reagents on a resin can be generated readily by using an iodine– or bromine–magnesium exchange.[19] Various functionalized iodobenzoic acids have been attached to Wang resins through the carboxy group. The immobilized ester **84**, when treated with excess *i*PrMgBr at −30°C for 15–30 min, generates the corresponding aryl magnesium compound **85** in high yield. It can be quenched successfully with a range of electrophiles and the resulting adduct, for example, 4-cyanobenzoic acid (**86**), is released from the resin by treatment with trifluoroacetic acid (Scheme 17). This method has an excellent generality and the



Scheme 17. Immobilized functionalized aryl magnesium reagents for combinatorial synthesis.

yields and purities (HPLC) of products obtained via immobilized organomagnesium reagents prepared by a halogen–magnesium exchange are usually excellent, thus allowing their application in combinatorial chemistry.[45,46]

Oshima and co-workers have shown that besides alkyl magnesium halides, lithium trialkyl magnesiates (R_3MgLi) readily undergo iodine– or bromine–magnesium exchange reactions.[47,48] Lithium trialkyl magnesiates are prepared by the reaction of an organolithium reagent (RLi; 2 equiv) with an alkyl magnesium halide (RMgX; 1 equiv) in THF at 0°C. Either 1 or 0.5 equivalents of the lithium magnesiate (Bu_3MgLi), relative to the aromatic halide (X = I or Br), can be used, which shows that two of the three butyl groups undergo the exchange reaction. Thus, the reaction of 3-bromobenzonitrile (**87**) provides the lithium diaryl butylmagnesiate **88**, which is allylated in the presence of CuCN·2 LiCl[24] to give the nitrile **89** in 85% yield (Scheme 18). The



Scheme 18. Br/Mg exchange for the preparation of functionalized aryl magnesium reagents.

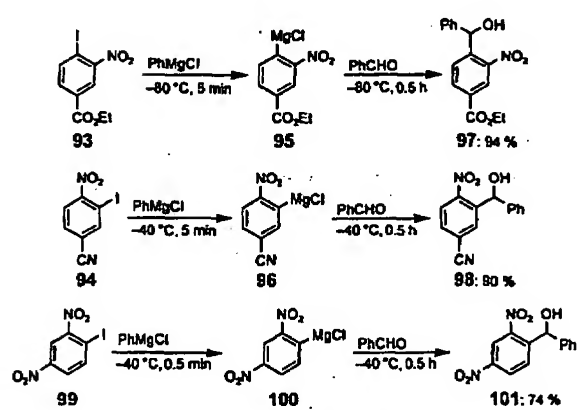
exchange reaction with lithium trialkyl magnesiates is generally faster than the halogen–magnesium exchange reaction with iPrMgBr and is less sensitive to the electronic density of the aromatic ring. Importantly, trialkyl magnesiates react more rapidly with aryl bromides than does iPrMgCl. However, the resulting lithium triorganomagnesiates of type **88** are more sensitive to the presence of electrophilic functional groups and thus exhibit a reactivity that is intermediate between organolithium and organomagnesium species. Therefore, the greater reactivity limits the number of functional groups usually tolerated in these exchange reagents.

The presence of an extra butyl group in **88** may also complicate the quenching of the reactions owing to competitive reactivity with electrophiles. However, Bu_3MgLi is an excellent reagent for preparing functionalized biaryl compounds of type **90**. Thus, lithium tributylmagnesiate induced bromine–magnesium exchange of the amide **91** provides the magnesiate species **92**, which undergoes a smooth titanium(IV)-mediated homocoupling reaction, leading to the biphenyl derivative **90** in 72% yield (Scheme 18).[49]

2.3. Reactions of Nitroarene Derivatives with Organomagnesium Reagents

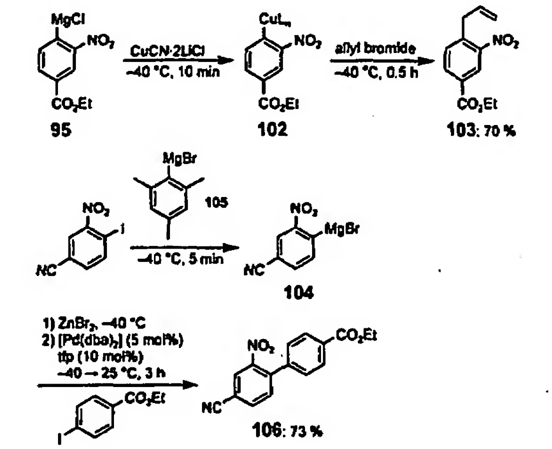
The reaction of nitroarenes with Grignard reagents was first investigated in the pioneering work of Wieland in 1903.[50] Several reactions between nitroaromatic and organometallic compounds were carefully investigated by Bartoli and co-workers.[51] Owing to the high electrophilicity of the nitro functionality, organometallic species can trigger either nucleophilic attack or electron-transfer reactions. However, it has been shown that *ortho*-lithiated nitrobenzene is stable at very low temperature.[52] Interestingly, the corresponding zinc and copper species obtained by transmetallation with zinc(II) or copper(I) salts, exhibit excellent stability and show, under appropriate reaction conditions, no tendency to undergo electron-transfer reactions.[53]

A broad range of functionalized aryl magnesium compounds that bear a nitro function at the *ortho* position can be prepared by iodine–magnesium exchange.[54] Thus, the nitro-substituted aryl iodides **93** and **94** undergo a smooth I/Mg exchange with phenylmagnesium chloride within a few minutes at −80 and −40°C, respectively, leading to the expected Grignard reagents **95** and **96**. After the addition of benzaldehyde, the benzylic alcohols **97** and **98** are obtained respectively in 94% and 90% yields.[54] Even an electron-poor aryl iodide such as the dinitro derivative **99** cleanly provides the corresponding Grignard reagent **100**, which reacts with benzaldehyde to give the benzylic alcohol **101** in 74% yield (Scheme 19).



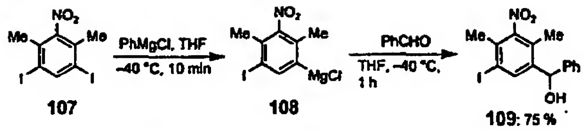
Scheme 19. Preparation of polyfunctionalized aryl magnesium compounds bearing a nitro function.

Transmetallation of the Grignard reagent **95** with CuCN·2 LiCl[24] furnishes the corresponding copper reagent **102**, which can be trapped by several electrophiles, such as acyl halides or allylic halides, to afford products of type **103** (Scheme 20).[54] These results indicate that, contrary to



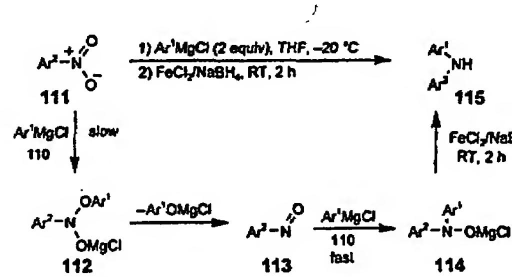
Scheme 20. Transmetallation of nitro-substituted aryl magnesium compounds. dba = Dibenzylideneacetone, tfp = tri-*ortho*-furylphosphane.

general belief, single-electron-transfer reactions between nitro groups and organometallic species, especially organomagnesium compounds, is less favorable than the halogen–magnesium exchange reaction. Palladium(0)-catalyzed Negishi cross-coupling[55] can be performed by converting the magnesium reagents into the corresponding zinc reagents. The nitro-substituted aryl magnesium species **104** is best prepared by using the sterically hindered mesitylmagnesium bromide (**105**). Thus, the reaction of the zinc derivative of **104** with ethyl *p*-iodobenzoate (THF, −40°C→RT, 3 h) in the presence of $[Pd(dba)_2]$ (5 mol%) and tri-*o*-furylphosphane (10 mol%)[56] provides the biaryl compound **106** in 73% yield (Scheme 20).[54] The *ortho* relationship between the carbon–magnesium bond and the nitro function is essential for a clean and fast exchange reaction. *Meta*- and *para*-substituted iodonitroarenes lead to unselective reactions with addition of the organometallic species to the nitro group. The *o*-nitro-substitution pattern facilitates the I/Mg exchange by precomplexation of the Grignard reagent to the nitro function prior to I/Mg exchange. I/Mg exchange of *meta*- and *para*-substituted iodonitroarenes is only possible in cases in which the nitro group is sterically hindered. Thus, the reaction of the diiodonitrobenzene derivative **107** with PhMgCl (THF, −40°C, 10 min) furnishes the corresponding Grignard compound **108**, that reacts with benzaldehyde to afford the expected benzylic alcohol **109** in 75% yield (Scheme 21).[57]



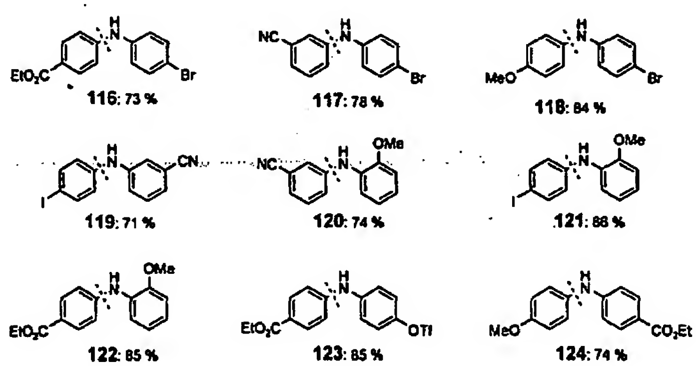
Scheme 21. Preparation of *meta*-nitroaryl magnesium compounds.

In the absence of sterically hindered systems such as **107**, phenylmagnesium chloride reacts with nitroarenes.[50,51] This reaction proceeds according to the mechanism originally proposed by Köbrich and co-workers (Scheme 22).[52a] The aryl magnesium reagent **110** adds first to the oxygen atom of



Scheme 22. Mechanism of the reaction of aryl magnesium compounds with nitroarenes leading to diaryl amines.

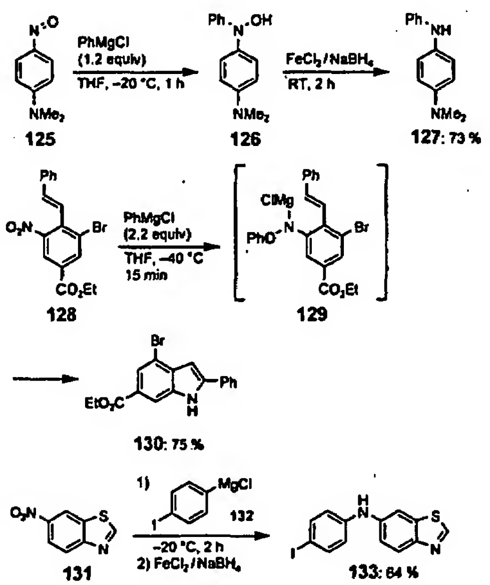
the nitro function of arene **111** to furnish the adduct **112**, which eliminates one equivalent of a magnesium phenolate (Ar^1OMgCl), providing the arylnitroso derivative **113**. The addition of a second equivalent of Ar^1MgCl to **113** furnishes the magnesium salt of a diaryl hydroxylamine **114**. Diaryl hydroxylamines are air-sensitive and difficult to isolate in pure form. To make this reaction of preparative interest, a subsequent reduction with $FeCl_2/NaBH_4$ is required, providing the diaryl amine **115** (Scheme 22).[58] The method allows arylation of nitrobenzene derivatives and therefore is ideal for preparing a range of functionalized diaryl amines such as **116–124** (Scheme 23).[59] This reaction complements recently developed palladium(0)-catalyzed amination reactions[60] and



Scheme 23. Polyfunctionalized diaryl amines obtained by the reaction of a functionalized aryl magnesium compound with nitroarenes. The dotted lines indicate the newly formed C–N bond.

related amination procedures that use a copper(I)[61] or nickel(0)[62] catalysis. As indicated above, the mild reaction conditions are compatible with a range of functional groups.

The Grignard reagent can bear electron-withdrawing groups (**116, 117, 120, 122, 123**) or electron-donating groups (**118, 124**). The same remark is true for the nitroarene. Interestingly, sensitive functions such as an iodine, bromine, or triflate[59] group can be present in either reaction partner, which is normally problematic in transition-metal-catalyzed amination procedures.[60–62] As shown in the mechanistic pathway described in Scheme 22, 2 equivalents of the aryl magnesium compound are required to produce amines of type **115**; 1 equivalent of the aryl magnesium reagent is wasted in the formation of the magnesium phenolate. This can be avoided by using a nitrosoarene instead of a nitroarene as the electrophilic reagent. The reaction of 4-dimethylaminonitrosobenzene (**125**) with PhMgCl (1.2 equiv) provides the expected[63,64] diaryl hydroxylamine **126**, which after reductive treatment ($FeCl_2/NaBH_4$), gives the diaryl amine **127** in 73% yield (Scheme 24). Sterically hindered, electron-poor nitroarenes such as **128** react with PhMgCl to generate an aryl

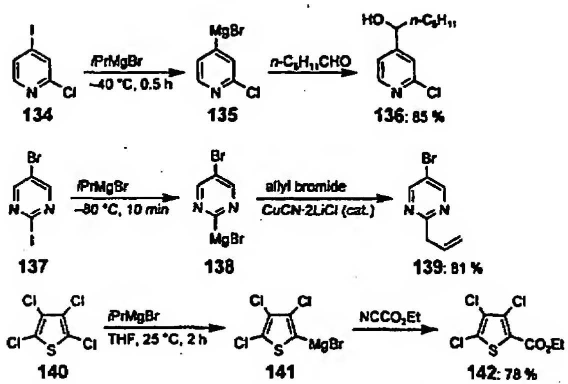


Scheme 24. The reaction of aryl magnesium reagents with nitro- and nitrosoarenes.

nitroso intermediate, which undergoes a reaction at the oxygen atom of the nitroso functional group, providing a magnesium nitrenoid[65] of type **129**. An intramolecular C–H insertion is triggered to give the polyfunctionalized indole **130** in 75% yield.[66] Finally, the reaction of heterocyclic benzothiazoles **131** with functionalized aryl magnesium species **132** provides the functionalized heterocycle **133** in 64% yield (Scheme 24).[59]

2.4. Preparation of Functionalized Heteroaryl Magnesium Reagents

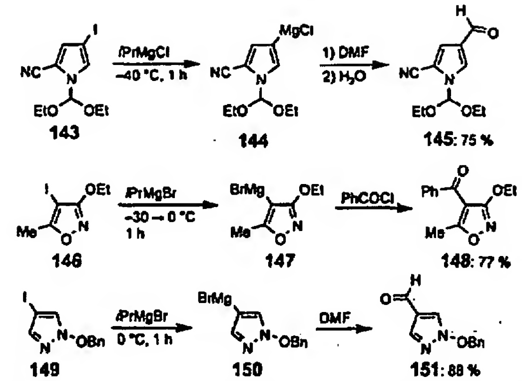
A variety of functionalized heterocyclic Grignard reagents can be prepared by using an iodine– or bromine–magnesium exchange reaction.[32,67] The electronic nature of the heterocycle influences the halogen–magnesium exchange rate: electron-poor heterocycles react faster and electron-withdrawing substituents strongly accelerate the exchange. 2-Chloro-4-iodopyridine (**134**) reacts with *i*PrMgBr at −40°C within 30 min[32,68] to furnish selectively the magnesium species **135**. The latter species adds to hexanal, leading to the alcohol **136** in 85% yield (Scheme 25). If instead of a



Scheme 25. The rate of the halogen–magnesium exchange reaction is dependent on the nature of the heterocycle.

pyridine, a pyrimidine derivative such as **137** is used, a selective iodine–magnesium exchange occurs at −80°C within 10 min, providing the organomagnesium compound **138**. The subsequent reaction of **138** with allyl bromide in the presence of CuCN·2 LiCl[24] gives the 2-allylpyrimidine **139** in 81% yield.[32] Although a chlorine–magnesium exchange is a very slow reaction, the presence of four chlorine atoms in tetrachlorothiophene (**140**) accelerates this exchange (25°C, 2 h), leading to the magnesiated heterocycle **141**, which reacts with ethyl cyanoformate to provide the thienylester **142** in 78% yield (Scheme 25).[32b]

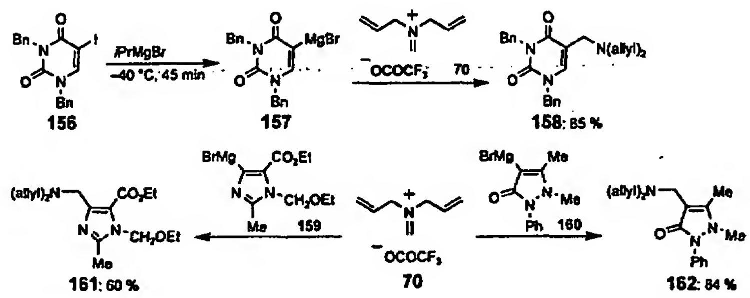
A range of functionalized iodoheterocycles have been magnesiated through an iodine–magnesium exchange, thus allowing a rapid synthesis of polyfunctionalized heterocycles.[69,70] Thus, the protected iodopyrrole **143** undergoes an iodine–magnesium exchange at −40°C within 1 h, leading to the magnesiated pyrrole **144**, which reacts with DMF to furnish the formyl derivative **145** in 75% yield (Scheme 26).[71] 4-Iodo-3-ethoxy-5-methylisoxazole (**146**) is converted into the corresponding Grignard reagent **147**, which reacts directly with benzoyl chloride to give the ketone **148** in 77% yield.[72] Also 4-iodopyrazoles such as **149** are converted at 0°C into the intermediate organomagnesium reagent **150**. The subsequent reaction of **150** with DMF furnishes the formylated derivative **151** in 88% yield (Scheme 26).[73]



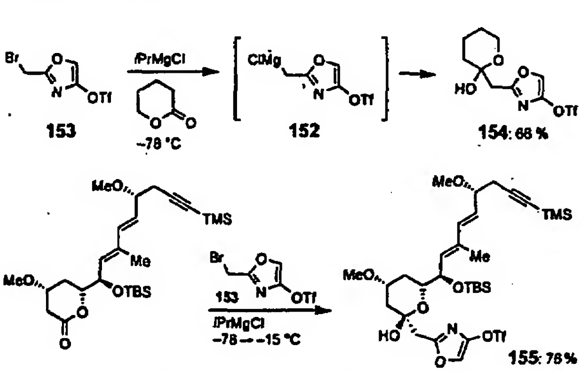
Scheme 26. Magnesiation of five-membered heterocycles. DMF = N,N-dimethylformamide.

Sensitive heterocyclic "benzylic" magnesium species such as **152** are readily obtained by a bromine–magnesium exchange from the bromomethyloxazole **153** (Scheme 27). Grignard reagent **152** is generated at −78 °C in the presence of δ-valerolactone (to minimize self-condensation), leading to the hemiketal **154** in 66% yield. This reaction was used to prepare advanced building blocks such as **155** for the total synthesis of (+)-phorboxazole A (Scheme 27).[74]

The preparation of functionalized uracils is of interest owing to the potential biological properties of this important class of heterocycles.[75] Starting from various protected 5-iodouracils such as **156**, the addition of *i*PrMgBr (−40 °C, 45 min) leads to the formation of the corresponding magnesium compound **157**, which can be trapped by various aldehydes, ketones, and acid chlorides. The use of the iminium salt **70**[39,40] leads to the diallylaminomethyl product **158** in 85% yield (Scheme 28).[76] Various magnesiated imidazoles such as **159** or antipyrines such as **160** react with the iminium reagent **70** to afford the diallylaminomethylated products **161** and **162**, respectively, in satisfactory yields.[77]

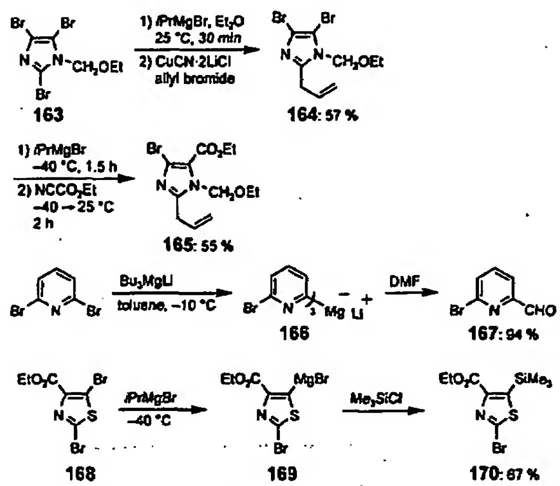


Scheme 28. Aminomethylation of heterocyclic magnesium reagents.



Scheme 27. Preparation of (+)-phorboxazole A intermediates by using a Br/Mg exchange. TMS = trimethylsilyl.

Polyhalogenated substrates usually undergo a single, selective halogen–magnesium exchange (Scheme 29). After the first magnesiation, the electron density of the heterocycle increases to such an extent that a subsequent second exchange is very slow. This very general behavior leads to the high chemoselectivity of the Br/Mg exchange reaction. The first exchange reaction of tribromoimidazole **163**[78] occurs at C2. Copper-catalyzed allylation leads to the 4,5-dibromoimidazole **164** (Scheme 29). Treatment of **164** with a second equivalent of *i*PrMgBr leads to an exchange reaction only at C5, as the intermediate Grignard reagent is stabilized by chelation. After quenching with ethyl cyanoformate (−40→25 °C, 2 h), the corresponding 4-bromo-5-carbethoxyimidazole **165** is obtained in 55% yield (Scheme 29).[32] The presence of chelating groups strongly influences the regioselectivity of the Br/Mg exchange. Thus, the dibromothiazole

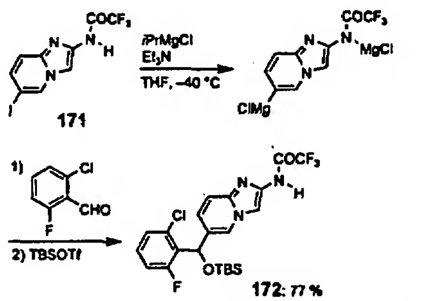


Scheme 29. Regioselective Br/Mg-exchange reactions.

168 undergoes a selective exchange at C5 owing to the chelating effect of the ethoxycarbonyl group, leaving the bromide at C2 unaffected. The reaction of the intermediate Grignard reagent **169** with Me_3SiCl provides the expected product **170** in 67% yield (Scheme 29).[32b] This selectivity has been used to convert 4,5-diiodoimidazoles into the corre-

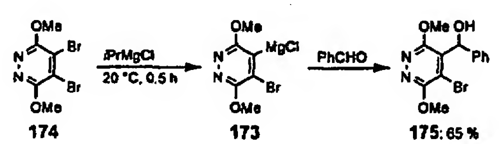
sponding 4-iodoimidazoles by using an I/Mg exchange followed by protonation.[79] Similarly, 2,6-dibromopyridine has been selectively exchanged with *i*PrMgX to generate the monomagnesium species.[32,80] The use of the magnesiate species Bu_3MgLi proves to be advantageous for performing this exchange reaction, leading to the ate complex **166**, which rapidly reacts with DMF to furnish the aldehyde **167** in 94% yield.[81] The use of magnesiate reagents for the preparation of various pyridyl magnesium species generally requires 1 equivalent of $BuMe_2MgLi$.[48]

Imidazo[1,2-*a*]pyridines are potentially a pharmaceutically useful class of heterocycles. The preparation of a range of functionalized 2-aminoimidazo[1,2-*a*]pyridines of type **172** has been realized starting from the heterocyclic iodide **171** and performing an I/Mg exchange at −40°C (Scheme 30).[82]



Scheme 30. Preparation of imidazo[1,2-*a*]pyridines by using a I/Mg-exchange reaction.

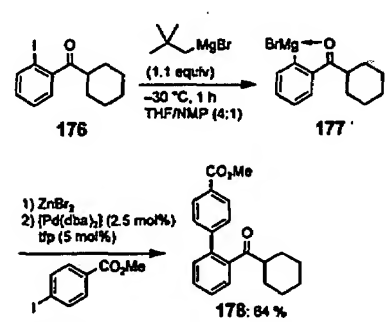
Quéguiner and co-workers have developed reaction conditions that allow the synthesis of magnesiated diazines such as **173**. The addition of *i*PrMgCl to the 4,5-dibromopyridazine **174** at 20°C furnishes, within 1 h, the heterocyclic magnesium species **173**, which affords a range of new functionalized pyridazines such as **175** after quenching with an electrophile (Scheme 31).[80b]



Scheme 31. Magnesiation of pyridazine derivatives through a Br/Mg-exchange reaction.

Finally, a number of these heterocyclic Grignard reagents can be generated with solid-phase reagents and reacted with typical electrophiles in excellent yield.[19] As numerous heterocyclic bromides are available, this exchange method is anticipated to become a major method for the functionalization of sensitive polyfunctionalized heterocycles. The carbon–magnesium bond possesses a good intrinsic reactivity, which can be enhanced by appropriate transmetallations. The presence of electron-poor substituents attached to the heterocyclic ring somewhat reduces the reactivity of a neighboring carbon–magnesium bond and further improves the functional-group compatibility of this carbon–metal bond.

How far can this functional group tolerance be extended? A keto group usually reacts with a Grignard reagent, even at −70°C. In fact, *i*PrMgCl reacts with benzophenone to afford the addition product and a large amount of diphenylmethanol, which results from a β-hydrogen reductive transfer. Nevertheless, by tuning the reaction conditions, the preparation of ketone-containing aryl magnesium species can be achieved. To avoid side reactions, a sterically hindered but reactive Grignard reagent was chosen: neopentylmagnesium bromide (NpMgBr)[83] in conjunction with *N*-methylpyrrolidinone (NMP) as a polar cosolvent to increase the rate of the iodine–magnesium exchange. Based on these modifications, 2-iodophenyl cyclohexyl ketone (**176**) reacts with NpMgBr (1.1 equiv) at −30°C within 1 h in THF/NMP (4:1) to afford the aryl magnesium reagent **177** (Scheme 32). The *ortho*-keto

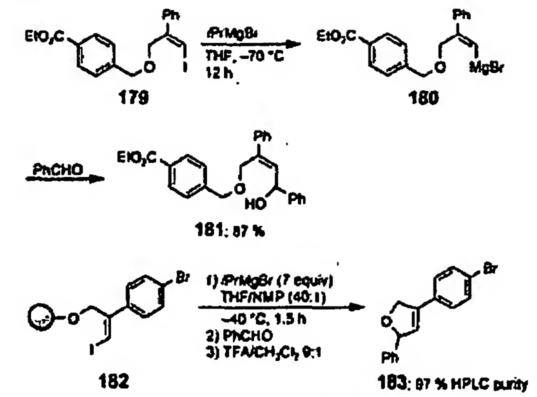


Scheme 32. Preparation of the aryl magnesium compound **177** bearing a keto group.

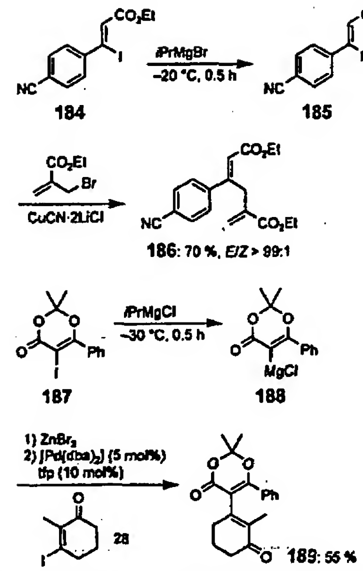
function facilitates formation of the Grignard reagent by precoordination of NpMgBr and stabilizes the resulting aryl magnesium species by chelation. Transmetallation of **177** with $ZnBr_2$ followed by Negishi cross-coupling,[55] furnishes the ketoester **178** in 64% yield (Scheme 32).[84]

2.5. *Preparation of Functionalized Alkenyl Magnesium Reagents*

Alkenyl iodides undergo I/Mg exchange upon reaction with *i*PrMgBr or iPr_2Mg. However, this exchange reaction is slower than with aryl iodides. Thus, (*E*)-1-iodo-1-octene only undergoes the exchange reaction at 25°C and the reaction requires 18 h, therefore precluding the presence of functionality at a remote position in iodoalkenes.[85] However, the presence of a chelating heteroatom or of an electron-withdrawing functionality directly linked to the double bond greatly enhances its propensity for undergoing iodine–magnesium exchange. Thus, the functionalized *Z* allylic ether **179** reacts at −78°C with *i*PrMgBr, providing the corresponding alkenyl magnesium reagent **180**. The reaction of **180** with PhCHO gives the *Z* alcohol **181** in 87% yield (Scheme 33).[85] Similarly, the resin-attached allylic ether **182** reacts smoothly with *i*PrMgBr in THF/NMP (40:1) within 1.5 h at −40°C, leading to the desired Grignard reagent. In the absence of



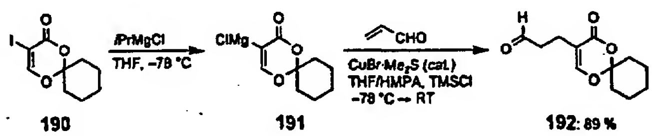
Scheme 33. Preparation of functionalized alkenyl magnesium reagents. TFA = trifluoroacetic acid.



Scheme 34. Preparation of carbonyl-containing alkenyl magnesium compounds.

NMP, the exchange reaction is considerably slower. Quenching with benzaldehyde and cleavage from the resin with TFA in CH_2Cl_2 provides the dihydrofuran **183** (97% purity).[85,46b]

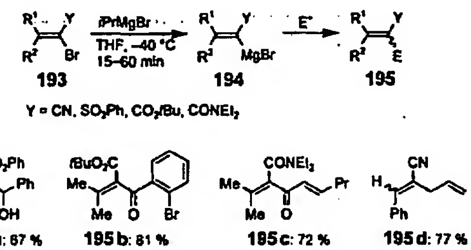
The presence of an electron-withdrawing group attached to the double bond considerably facilitates the iodine–magnesium exchange reaction. A range of β-iodoenoates such as **184** are converted into the corresponding Grignard reagent **185** (−20°C, 30 min). The reaction with an allylic bromide in the presence of CuCN·2 LiCl[24] leads to the *E* enoate **186**, which demonstrates a high configurational stability of the intermediate alkenyl magnesium species **185**.[86] Whereas alkenyl magnesium compounds that bear a leaving group such as a halide or an alkoxide at the β position are elusive reagents,[87] the incorporation of the leaving group in a ring system leads to more robust reagents. The reaction of **187** with *i*PrMgCl at −30°C furnishes the desired Grignard reagent **188**, which has a half-life of ≈2 h at −30°C. After transmetallation with $ZnBr_2$, **188** undergoes a smooth Negishi cross-coupling with 3-iodo-2-methyl-cyclohex-2-enone (**28**), leading to the enone **189** in 55% yield (Scheme 34).[88,89] The preparation of related carbonyl-containing alkenyl magnesium reagents was reported by Hiemstra and co-workers in the course of synthetic studies toward the synthesis of solanoeclepin A.[90,91] Treatment of the cyclic alkenyl iodide **190** with *i*PrMgCl in THF at −78°C furnished the desired Grignard reagent **191**, which reacts with acrolein and catalytic CuBr·Me_2S in THF/HMPA in the presence of TMSCl to furnish the Michael adduct **192** in 89% yield (Scheme 35).[91]



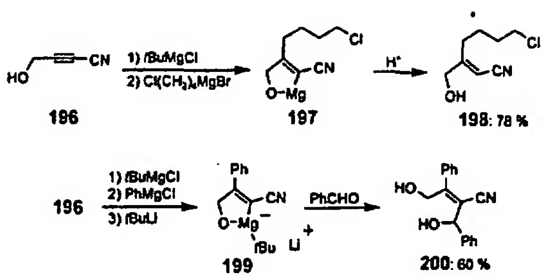
Scheme 35. Copper-catalyzed Michael addition of a functionalized alkenyl magnesium reagent. HMPA = hexamethylphosphoramide.

If the sp^2-hybridized carbon atom bears an electron-withdrawing group *and* a bromine atom, a very fast Br/Mg exchange reaction is usually observed (−40°C, 15–60 min). This behavior is very general for alkenyl bromides of type **193** (Y = CN, SO_2Ph, CO_2tBu, and $CONEt_2$), which readily react with *i*PrMgBr to affording Grignard reagents of type **194**. The reaction of **194** with electrophiles is not always stereoselective,[92] and produce a mixture of diastereoisomers of type **195**, although this method provides an efficient synthesis of tri- and tetrasubstituted alkenes **195a–d** (Scheme 36).[93,94]

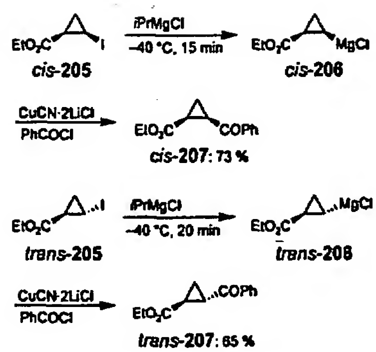
Remarkably, the conjugate addition of various Grignard reagents to the alkynyl nitrile **196** generates the stabilized and unreactive cyclic magnesium chelate **197**, which after protonation furnishes the polyfunctionalized nitrile **198** (Scheme 37). Fleming et al. showed that the reactivity of cyclic organomagnesium reagents of the type **197** can be dramatically enhanced by generating an intermediate magnesiate species **199**. This magnesiate species now reacts with PhCHO, leading to the allylic diol **200** in 60% yield with complete retention of the stereochemistry of the double bond (Scheme 37).[95]



Scheme 36. Functionalized alkenyl magnesium compounds bearing an electron-withdrawing group at the α position.

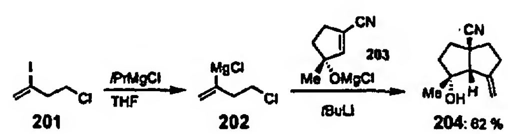


Scheme 37. Functionalized alkenyl magnesium compounds obtained by carbomagnesiation of an alkyne.

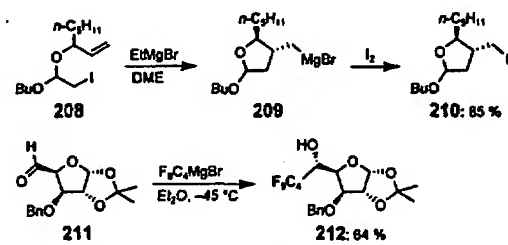


Scheme 39. Stereoselective preparation of functionalized cyclopropyl magnesium compounds.

The I/Mg exchange of 2-iodo-4-chloro-1-butene (**201**) provides a functionalized alkenyl magnesium species **202**, which reacts in a highly diastereoselective manner with the magnesiated unsaturated nitrile **203** to provide the interesting bicyclic product **204** in 62% yield (Scheme 38).[95]



Scheme 38. Functionalized alkenyl magnesium compounds obtained by I/Mg exchange.



Scheme 40. Reactions of functionalized alkyl magnesium compounds.

2.6. Functionalized Alkyl Magnesium Reagents

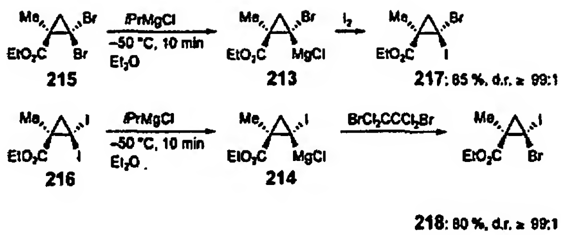
Although the preparation of polyfunctionalized alkyl magnesium reagents may be envisioned, only a few examples have been reported.[96] The difficulties arise from the higher reactivity of the resulting alkyl magnesium compounds relative to that of alkenyl–, aryl–, or heteroaryl–magnesium species. Also, the rate of the iodine–magnesium exchange seems to be slower for alkyl derivatives. However, a range of polyfunctionalized cyclopropyl magnesium compounds can be prepared by iodine–magnesium exchange.[97] Thus, the cyclopropyl iodoesters *cis*-**205** and *trans*-**205** are readily converted into the corresponding Grignard reagents *cis*-**206** and *trans*-**206**, respectively. The formation of the magnesium organometallics **206** is stereoselective, and their reaction with benzoyl chloride furnishes, after transmetallation of **206** with CuCN·2 LiCl,[24] the expected *cis*- and *trans*-1,2-ketoesters **207** in 73% and 65% yields, [97] respectively, with retention of configuration[98,99] (Scheme 39).

Interestingly, the radical cyclization of allylic β-iodoacetals of type **208** was shown by Oshima and co-workers to provide the corresponding organomagnesium compound **209** in DME, which leads after iodolysis to the primary alkyl iodide **210** (Scheme 40).[96] Formation of perfluorinated alkyl Grignards is achieved through an exchange at low temperature in diethyl ether.[100] Perfluorinated Grignard reagents were recently used to functionalize a range of sugar derivatives such as **211**, leading to the fluorinated sugar derivatives of type **212** in 64% yield with high stereoselectivity (Scheme 40).[101]

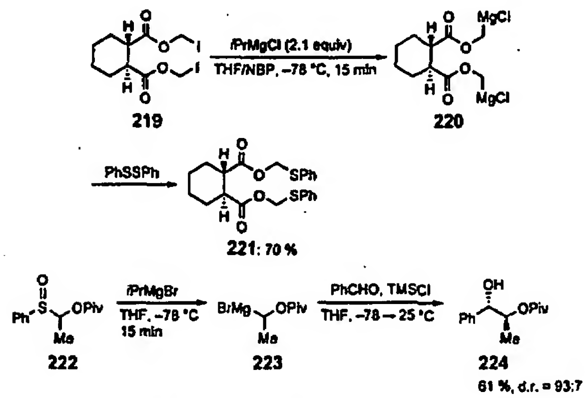
2.7. Functionalized Magnesium Carbenoids

A pioneering bromine–magnesium exchange by Villieras et al.[13] allows the general preparation of magnesium carbenoids.[14] A fast reaction allows the preparation of sensitive cyclopropyl magnesium carbenoids such as **213** and **214**, starting from the corresponding 1,1-dihalocyclopropanes **215** and **216**. By performing the halogen–magnesium exchange in diethyl ether, a completely stereoselective exchange reaction is observed. Quenching of the magnesium carbenoids proceeds with retention of configuration, providing the two diastereomeric products **217** and **218**, respectively, in yields of 80 and 85%, respectively (Scheme 41).[97]

Functionalized acyclic magnesium carbenoids can be prepared in THF/NBP mixtures at low temperatures. Thus, the reaction of the bisiodomethylcarboxylate **219** with *i*PrMgCl in THF/NBP is complete within 15 min at −78°C.[102] The resulting chiral biscarbenoid **220** is quenched with PhSSPh to give the bisadduct **221** in 70% yield (Scheme 42).[102] Substituted magnesium carbenoids were prepared by using a sulfinyl/magnesium exchange reaction recently introduced by Satoh et al.[103] Thus, the reaction of the sulfoxide **222** with *i*PrMgBr at −78°C furnishes the desired magnesium carbenoid **223**, which reacts with PhCHO



Scheme 41. Stereoselective preparation of cyclopropyl magnesium carbenoids.

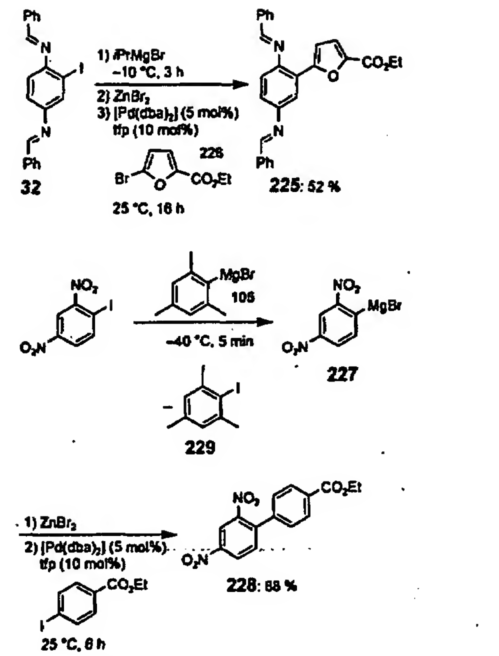


Scheme 42. Preparation of functionalized acyclic magnesium carbenoids. NBP = *N*-butylpyrrolidinone.

with excellent diastereoselectivity, providing the monoprotected 1,2-diol **224** in 61 % yield (d.r. = 93:7) (Scheme 42).[103]

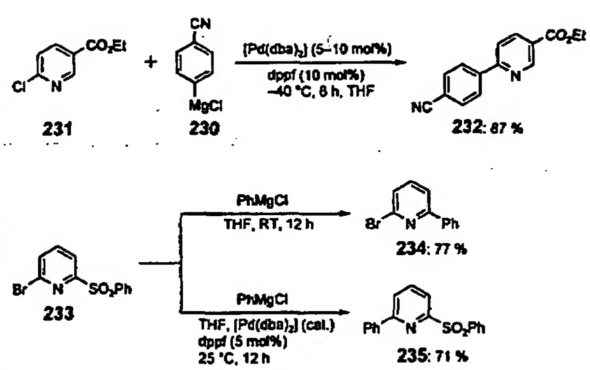
2.8. *Functionalized Magnesium Reagents in Cross-Coupling*

The availability of functionalized Grignard reagents considerably enhances the scope of these reagents for performing cross-coupling reactions. Especially interesting are aryl magnesium reagents that bear amino groups.[20,104] A range of 2-aryl-1,4-phenylenediamines of type **225** can be prepared starting from the bisimine **32**; the I/Mg exchange is complete within 3 h at −10 °C. After transmetallation to the zinc reagent with $ZnBr_2$, $[Pd(dba)_2]$ (5 mol %), tfp (10 mol %), and ethyl 5-bromo-2-furoate (**226**) are added. The cross-coupling reaction is usually complete after 16 h at 25 °C, leading to the 1,4-phenylenediamine **225** in 52 % yield (Scheme 43).[104] Nitro-containing Grignard reagents such as **227**, which are prepared through iodine–magnesium[54] exchange in THF with mesitylmagnesium bromide (**105**), smoothly undergo Negishi cross-coupling reactions, leading to polyfunctionalized nitroarenes **228**. The mesityl iodide (**229**), which is generated in the iodine–magnesium exchange reaction, is unreactive under the conditions used in these cross-couplings (Scheme 43).[105]



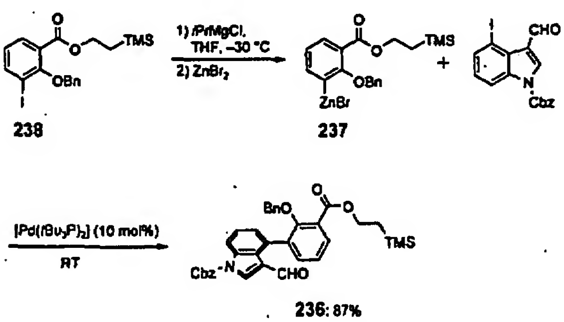
Scheme 43. Cross-coupling with nitrogen-functionalized Grignard reagents.

Functionalized Grignard reagents such as **230** directly undergo cross-coupling reactions with various 2-halopyridines **231** in the presence of Pd^0 catalysts. These remarkably fast cross-coupling reactions required the presence of a Pd^0 catalyst and are therefore not direct addition–elimination reactions of the Grignard reagent. The corresponding aryl zinc reagents also react more slowly. These reactions may proceed through the formation of an organopalladate[106] of the type $[MgX]^+[ArPdL_2]^-$, which undergo a fast addition–elimination reaction with the 2-chloropyridine derivative **231**, leading to the functionalized pyridine **232** in 87 % yield (Scheme 44).[107] This reaction can be extended to several haloquinolines.[108]



Scheme 44. Pd-catalyzed cross-coupling with 2-halopyridines. dppf = 1,1′-Bis(diphenylphosphanyl)ferrocene.

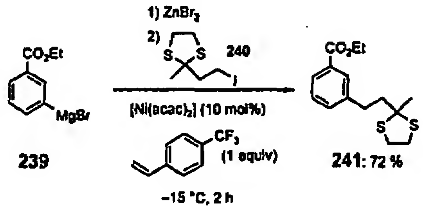
Quéguiner and co-workers found an interesting selectivity[108] in the cross-coupling of bromosulfone 233. Thus, PhMgCl reacts with the disubstituted pyridine 233 by direct substitution of the phenylsulfonyl group, leading to the bromopyridine 234 in 77% yield (Scheme 44). However, the use of a palladium catalyst allows the preparation of highly functionalized biaryl compounds of type 235.[109] Analogously, the polyfunctionalized zinc reagent 237, which is obtained from the iodide 238 through I/Mg exchange followed by transmetallation, reacts readily in the presence of the highly active palladium catalyst $[Pd(tBu_3P)_2]$[110] under mild conditions to furnish the biaryl compound 236 in 87% yield (Scheme 45).



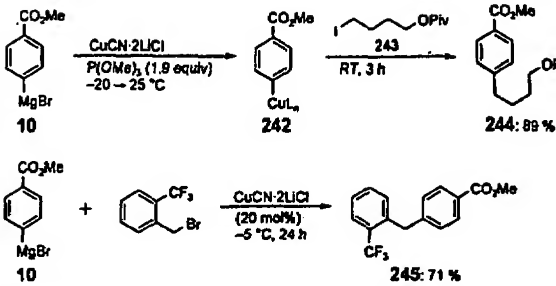
Scheme 45. Pd-catalyzed cross-coupling of highly functionalized aryl zinc reagents. Cbz = benzyloxycarbonyl.

The cross-coupling of functionalized aryl zinc compounds, obtained by transmetallating the corresponding magnesium reagents, can be accomplished by using $[Ni(acac)_2]$ (10 mol%) as the catalyst in the presence of 4-trifluoromethylstyrene or 4-fluorostyrene as promoter of the reductive elimination step. Under these conditions, the Grignard reagent 239 reacts with the iodothioketal 240, providing the desired cross-coupling product 241 in 72% yield (Scheme 46).[111]

An alternative to this Ni-catalyzed reaction is the corresponding copper-mediated reaction. In this case, the functionalized aryl magnesium species is transmetallated to the corresponding aryl copper reagent with CuCN·2 LiCl[24] in the presence of trimethylphosphite (Scheme 47). This last additive confers an excellent stability to the copper reagent, which can be handled at room temperature under these conditions. Thus, the reaction of the magnesium species 10



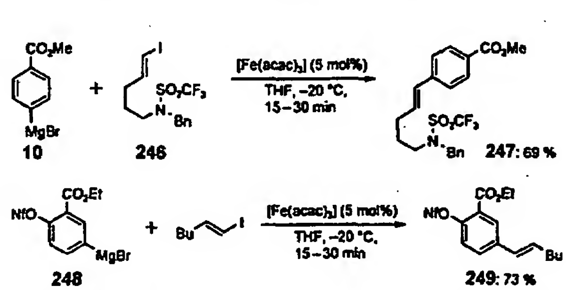
Scheme 46. Ni-catalyzed cross-coupling between functionalized Grignard reagents and functionalized alkyl iodides.



Scheme 47. Cu-mediated cross-coupling reactions of functionalized aryl magnesium compounds. Piv = pivaloyl.

with CuCN·2 LiCl[24] and $P(OMe)_3$ furnishes the stable aryl copper 242, which undergoes a smooth cross-coupling reaction with functionalized alkyl iodides such as the iodopivalate 243, leading to the substitution product 244 in 89% yield.[112] Interestingly, reactive benzylic halides undergo the cross-coupling reaction in the presence of a catalytic amount of CuCN·2 LiCl,[24] leading to diaryl methane derivatives such as 245 (Scheme 47).[112]

The low cost and low toxicity of iron(III) salts have allowed these complexes to be used with success in several cross-coupling procedures.[113,114,115] Functionalized aryl magnesium species undergo efficient cross-coupling reactions with polyfunctionalized alkenyl iodides such as 246 in the presence of $[Fe(acac)_3]$ (5 mol%), leading to the styrene derivatives of type 247 in 69% yield. Remarkably, the cross-coupling reaction is complete at −20°C within 15–30 min (Scheme 48).[116] The aryl magnesium compound can bear



Scheme 48. Fe^{III}-catalyzed cross-coupling reactions with functionalized aryl magnesium species. acac = acetylacetone.

various electrophilic functions such as a nonaflate[117] (e.g. 248). The iron(III)-catalyzed cross-coupling reaction also proceeds smoothly, leading to the highly functionalized nonaflate 249 in 73% yield (Scheme 48).[116]

3. Summary and Outlook

The halogen-magnesium exchange reaction has opened new perspectives in organic synthesis. Many more functional groups than previously thought are compatible with organomagnesium reagents. The mild conditions required for

halogen–magnesium exchange are the key for assuring a high functional-group tolerance. This again places Grignard reagents in a central position in organic chemistry and opens fascinating new perspectives. The dramatic functional-group tolerance shows that organic chemists have only partially mastered the reactivity of organometallic reagents for the elaboration of complex organic molecules. More mild and general, environmentally and industrially friendly synthetic methods involving organometallic remain to be discovered.[118]

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[1] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* 2000, *112*, 4584; *Angew. Chem. Int. Ed.* 2000, *39*, 4415; b) C. Najera, M. Yus, *Recent Res. Dev. Org. Chem.* 1997, *1*, 67.
[2] a) R. D. Rieke, *Science* 1989, *246*, 1260; b) T. P. Burns, R. D. Rieke, *J. Org. Chem.* 1987, *52*, 3674; c) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* 2000, *65*, 5428.
[3] a) D. J. Ramon, M. Yus, *Eur. J. Org. Chem.* 2000, 225; b) C. Gomez, F. F. Huerta, M. Yus, *Tetrahedron* 1998, *54*, 1853, 6177; c) F. Foubelo, A. Gutierrez, M. Yus, *Tetrahedron Lett.* 1997, *38*, 4837; d) A. Guijarro, M. Yus, *Tetrahedron* 1995, *51*, 231; e) T. Cohen, M. Bhupathy, *Acc. Chem. Res.* 1989, *22*, 152; see also: f) M. Yus, R. P. Herrera, A. Guijarro, *Tetrahedron Lett.* 2001, *42*, 3455; g) I. Gomez, E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron* 2000, *56*, 4043.
[4] a) J. F. Normant, A. Alexakis, *Synthesis* 1981, 841; b) S. A. Rao, P. Knochel, *J. Am. Chem. Soc.* 1991, *113*, 5735.
[5] a) B. M. Trost, *Chem. Eur. J.* 1998, *4*, 2405; b) D. S. Mattesonin *The Chemistry of the Metal–Carbon Bond, Volume 4*, (Ed.: F. R. Hartley), Wiley, New York, 1987, p. 307.
[6] a) M.-X. Zhang, P. E. Eaton, *Angew. Chem.* 2002, *114*, 2273; *Angew. Chem. Int. Ed.* 2002, *41*, 2169; b) D. Hoppe, T. Heuse, *Angew. Chem.* 1997, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* 1997, *36*, 2282; c) T. A. Johnson, M. D. Curtis, P. Beak, *Org. Lett.* 2002, *4*, 2747; d) P. Beak, D. R. Anderson, M. D. Curtis, J. M. Laumer, D. J. Pippel, G. A. Weisenburger, *Acc. Chem. Res.* 2000, *33*, 715; e) S. Norsikian, I. Marek, J.-F. Normant, *Tetrahedron Lett.* 1997, *38*, 7523; f) C. Metallinos, V. Snieckus, *Org. Lett.* 2002, *4*, 1935; g) V. Snieckus, *Chem. Rev.* 1990, *90*, 879.
[7] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* 1938, *71*, 1903.
[8] a) R. G. Jones, H. Gilman, *Org. React.* 1951, *6*, 339; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* 1939, *61*, 106.
[9] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* 1976, *41*, 1187; b) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* 1975, *40*, 2394; c) W. E. Parham, L. D. Jones, *J. Org. Chem.* 1976, *41*, 2704; d) W. E. Parham, D. W. Boykin, *J. Org. Chem.* 1977, *42*, 260; e) W. E. Parham, R. M. Piccirilli, *J. Org. Chem.* 1977, *42*, 257; f) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* 1992, *114*, 3983.
[10] a) G. S. Silverman, P. E. Rakita in *Handbook of Grignard Reagents*, Marcel Dekker, New York, 1996; b) B. J. Wakefield in *Organomagnesium Methods in Organic Synthesis*; Academic Press, London, 1995; c) *Grignard Reagents: New Development*, (Ed.: H. G. Richey, Jr.), Wiley, New York, 1999.
[11] B. H. Lipshutz, S. Sengupta, *Org. Reactions* 1992, *41*, 135.
[12] C. Prévost, *Bull. Soc. Chim. Fr.* 1931, *49*, 1372.
[13] a) J. Villiéras, *Bull. Soc. Chim. Fr.* 1967, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* 1986, 470.
[14] For recent examples, see: a) A. Müller, M. Marsch, K. Harms, J. C. W. Lohrenz, G. Boche, *Angew. Chem.* 1996, *108*, 1639; *Angew. Chem. Int. Ed. Engl.* 1996, *35*, 1518; R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedron* 1994, *50*, 6049.
[15] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* 1971, *26*, 153.
[16] N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* 1987, *28*, 5845.
[17] a) D. J. Burton, Z. Y. Yang, *Tetrahedron* 1992, *48*, 189; b) R. D. Chambers, W. K. R. Musgrave, J. Savory, *J. Chem. Soc.* 1962, 1993.
[18] For other examples of halogen–magnesium exchange reactions, see: a) H. H. Paradies, M. Görbing, *Angew. Chem.* 1969, *81*, 293; *Angew. Chem. Int. Ed. Engl.* 1969, *8*, 279; b) G. Cahiez, D. Bernard, J. F. Normant, *J. Organomet. Chem.* 1976, *113*, 107; c) D. Seyferth, R. L. Lambert, *J. Organomet. Chem.* 1973, *54*, 123; d) H. Nishiyama, K. Isaka, K. Itoh, K. Ohno, H. Nagase, K. Matsumoto, H. Yoshiwara, *J. Org. Chem.* 1992, *57*, 407; e) C. Bolm, D. Pupowicz, *Tetrahedron Lett.* 1997, *38*, 7349.
[19] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* 1998, *110*, 1801; *Angew. Chem. Int. Ed.* 1998, *37*, 1701.
[20] A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* 2002, 565.
[21] P. Cali, M. Begtrup, *Synthesis* 2002, 63.
[22] R. Kober, W. Hammes, W. Steglich, *Angew. Chem.* 1982, *94*, 213; *Angew. Chem. Int. Ed. Engl.* 1982, *21*, 203; b) D. von der Brück, R. Bühler, H. Plieninger, *Tetrahedron* 1972, *28*, 791.
[23] T. Murafuji, K. Nishio, M. Nagasue, A. Tanabe, M. Aono, Y. Sugihara, *Synthesis* 2000, 1208.
[24] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* 1988, *53*, 2390.
[25] A. Staubitz, W. Dohle, P. Knochel, *Synthesis* 2003, 223.
[26] a) L. Gottlieb, A. I. Meyers, *Tetrahedron Lett.* 1990, *31*, 4723; b) A. I. Meyers, T. R. Elsworthy, *J. Org. Chem.* 1992, *57*, 4732; c) A. I. Meyers, G. Milot, *J. Am. Chem. Soc.* 1993, *115*, 6652.
[27] G. Varchi, A. E. Jensen, W. Dohle, A. Ricci, G. Cahiez, P. Knochel, *Synlett* 2001, 477.
[28] W. Dohle, PhD thesis, LMU München, 2002.
[29] D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel, *Org. Lett.* 2002, *4*, 1819.
[30] G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun.* 2003, 396.
[31] a) A. Casarini, P. Dembech, D. Lazzari, E. Marini, G. Reginato, A. Ricci, G. Seconi, *J. Org. Chem.* 1993, *58*, 5620; b) A. Alberti, F. Cane, P. Dembech, D. Lazzari, A. Ricci, G. Seconi, *J. Org. Chem.* 1996, *61*, 1677; c) F. I. Knight, J. M. Brown, D. Lazzari, A. Ricci, A. J. Blacker, *Tetrahedron* 1997, *53*, 11411; d) P. Dembach, G. Seconi, A. Ricci, *Chem. Eur. J.* 2000, *6*, 1281.
[32] a) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* 1999, *40*, 7449; b) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* 2000, *65*, 4618.
[33] T. Delacroix, L. Bérillon, G. Cahiez, P. Knochel, *J. Org. Chem.* 2000, *65*, 8108.
[34] J. Villiéras, M. Rambaud, *Synthesis* 1982, 924.

[35] A. Y. Fedorov, F. Carrara, J.-P. Finet, *Tetrahedron Lett.* **2001**, *42*, 5875.
[36] F. F. Kneisel, Y. Monguchi, K. M. Knapp, H. Zipse, P. Knochel, *Tetrahedron Lett.* **2002**, *43*, 4875.
[37] M. Poirier, F. Chen, C. Bernard, Y.-S. Wong, G. G. Wu, *Org. Lett.* **2001**, *3*, 3795.
[38] F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109.
[39] N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941.
[40] N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, 2143.
[41] a) M. T. Reetz, A. Kindler, *J. Chem. Soc. Chem. Commun.* **1994**, 2509; b) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 3368; c) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019; d) A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.* **1986**, *27*, 1047.
[42] G. Varchi, A. Ricci, G. Cahiez, P. Knochel, *Tetrahedron* **2000**, *56*, 2727.
[43] a) K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando, J. M. Ramanjulu, *Angew. Chem.* **1998**, *110*, 2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2717; b) K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li, R. Hughes, *Chem. Eur. J.* **1999**, *5*, 2622.
[44] K. S. Feldman, T. D. Cutarelli, *J. Am. Chem. Soc.* **2002**, *124*, 11600.
[45] a) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17.
[46] a) S. Marquais, M. Arlt, *Tetrahedron Lett.* **1996**, *37*, 5491; b) M. Rottländer, P. Knochel, *J. Comb. Chem.* **1999**, *1*, 181; for the preparation of organozinc reagents on a solid phase, see: c) Y. Kondo, T. Komine, M. Fujinami, M. Uchiyama, T. Sakamoto, *J. Comb. Chem.* **1999**, *1*, 123; d) R. W. F. Jackson, L. J. Oates, M. H. Block, *Chem. Commun.* **2000**, 1401.
[47] K. Oshima, *J. Organomet. Chem.* **1999**, *575*, 1.
[48] K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem.* **2000**, *112*, 2594; *Angew. Chem. Int. Ed.* **2000**, *39*, 2481; b) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; see also: c) R. I. Yousef, T. Rüffer, H. Schmidt, D. Steinborn, *J. Organomet. Chem.* **2002**, *655*, 111.
[49] A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *Tetrahedron* **2000**, *56*, 9601.
[50] a) H. Wieland, *Chem. Ber.* **1903**, *36*, 2315; b) H. Gilman, R. McCracken, *J. Am. Chem. Soc.* **1927**, *49*, 1052; c) T. Severin, R. Schmitz, *Chem. Ber.* **1963**, *96*, 3081; d) T. Severin, M. Adam, *Chem. Ber.* **1964**, *97*, 186.
[51] a) G. Bartoli, *Acc. Chem. Res.* **1984**, *17*, 109; b) G. Bartoli, M. Bosco, G. Cantagalli, R. Dalpozzo, F. Ciminale, *J. Chem. Soc. Perkin Trans. 2* **1985**, 773.
[52] a) G. Köbrich, P. Buck, *Chem. Ber.* **1970**, *103*, 1412; b) P. Buck, R. Gleiter, G. Köbrich, *Chem. Ber.* **1970**, *103*, 1431; c) P. Wiriyachitra, S. J. Falcone, M. P. Cava, *J. Org. Chem.* **1979**, *44*, 3957; d) J. F. Cameron, J. M. J. Fréchet, *J. Am. Chem. Soc.* **1991**, *113*, 4303.
[53] C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983.
[54] I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680; *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.
[55] a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) E. Negishi, H. Matsushita, M. Kobayashi, C. L. Rand, *Tetrahedron Lett.* **1983**, *24*, 3823; c) E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393; d) E. Negishi, Z. Owczarczyk, *Tetrahedron Lett.* **1991**, *32*, 6683.
[56] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585; b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905.
[57] I. Sapountzis, unpublished results.
[58] A. Ono, H. Sasaki, F. Yaginuma, *Chem. Ind. (London)* **1983**, 480.
[59] I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390.
[60] a) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125; b) J. P. Wolfe, S. Wagan, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2155; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; c) L. M. Alcazar-Roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-Sands, I. A. Guzei, *J. Am. Chem. Soc.* **2000**, *122*, 4618.
[61] a) A. Klapaus, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; b) M. Wolter, A. Klapaus, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803; c) R. Shen, J. A. Porco, Jr., *Org. Lett.* **2000**, *2*, 1333; d) A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **1999**, *64*, 2986.
[62] a) B. H. Lipshutz, H. Ueda, *Angew. Chem.* **2000**, *112*, 4666; *Angew. Chem. Int. Ed.* **2000**, *39*, 4492; b) C. Desmarets, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2001**, *42*, 247.
[63] F. Kopp, I. Sapountzis, P. Knochel, *Synlett*, **2003**, 885.
[64] a) N. Momiyama, H. Yamamoto, *Org. Lett.* **2002**, *4*, 3579; b) N. Momiyama, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 4666; *Angew. Chem. Int. Ed.* **2002**, *41*, 2986.
[65] a) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697; b) G. Boche, C. Boie, F. Bosold, K. Harms, M. Marsch, *Angew. Chem.* **1994**, *106*, 90; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 115; c) G. Boche, H. U. Wagner, *J. Chem. Soc. Chem. Commun.* **1984**, *23*, 1591.
[66] W. Dohle, A. Staubitz, P. Knochel, *Chem. Eur. J.* **2003**, *9*, in press.
[67] M. Rottländer, L. Boymond, L. Bérillon, A. Leprêtre, G. Varchi, S. Avolio, H. Laaziri, G. Quéguiner, A. Ricci, G. Cahiez, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 767.
[68] L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez, P. Knochel, *Synlett*, **1998**, 1359.
[69] I. Collins, *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2845.
[70] G. Quéguiner, F. Marsais, V. Snieckus, J. Epsztajin, *Adv. Heterocycl. Chem.* **1991**, *52*, 187.
[71] M. Bergauer, P. Gmeiner, *Synthesis* **2001**, 2281.
[72] H. Kromann, F. A. Slok, T. N. Johansen, P. Krogsgaard-Larsen, *Tetrahedron* **2001**, *57*, 2195.
[73] J. Felding, J. Kristensen, T. Bjerregaard, L. Sander, P. Vedso, M. Begtrup, *J. Org. Chem.* **1999**, *64*, 4196.
[74] A. B. Smith III, K. P. Minbiole, P. R. Verhoest, M. Schelhaas, *J. Am. Chem. Soc.* **2001**, *123*, 10942.
[75] G. R. Newkome, W. W. Pandler, *Contemporary Heterocyclic Chemistry*, Wiley, New York, **1982**.
[76] M. Abarbri, P. Knochel, *Synlett* **1999**, 1577.
[77] F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345.
[78] B. H. Lipshutz, W. Hagen *Tetrahedron Lett.* **1992**, *33*, 5865.
[79] a) C. J. Lovely, H. Du, H. V. R. Dias, *Org. Lett.* **2001**, *3*, 1319; see also: b) R. S. Loewe, S. M. Khersonsky, R. D. McCullough; *Adv. Mater.* **1999**, *11*, 250.
[80] a) F. Trécourt, G. Breton, F. Mongin, F. Marsais, G. Quéguiner, *Tetrahedron Lett.* **1999**, *40*, 4339; b) A. Leprêtre, A. Turck, N. Plé, P. Knochel, G. Quéguiner, *Tetrahedron* **2000**, *56*, 265.
[81] a) T. Mase, I. N. Houpis, A. Akao, I. Dorziotis, K. Emerson, T. Hoang, T. Iida, T. Itoh, K. Kamei, S. Kato, Y. Kato, M. Kawasaki, F. Lang, J. Lee, J. Lynch, P. Maligres, A. Molina, T. Nemoto, S. Okada, R. Reamer, J. Z. Song, D. Tschaen, T. Wada, D. Zewge, R. P. Volante, P. J. Reider, K. Tomimoto, *J. Org. Chem.* **2001**, *66*, 6775; b) T. Ida, T. Wada, K. Tomimoto, T. Mase, *Tetrahedron Lett.* **2001**, *42*, 4841.
[82] C. Jaramillo, J. C. Carretero, J. E. de Diego, M. del Prado, C. Hamdouchi, J. L. Roldán, C. Sánchez-Martínez, *Tetrahedron Lett.* **2002**, *43*, 9051.
[83] For the use of neopentyl organometallic reagents in zinc and copper organometallic chemistry, see: a) P. Jones, C. K. Reddy,

P. Knochel, *Tetrahedron* **1998**, *54*, 1471; b) P. Jones, P. Knochel, *J. Chem. Soc. Perkin Trans. 1*, **1997**, 3117.
[84] F. F. Kneisel, P. Knochel, *Synlett* **2002**, *11*, 1799.
[85] M. Rottländer, L. Boymond, G. Cahiez, P. Knochel, *J. Org. Chem.* **1999**, *64*, 1080.
[86] I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun.* **2001**, 2068.
[87] a) H. Gurien, *J. Org. Chem.* **1963**, *28*, 878; b) J. Ficini, J. C. Depezay, *Bull. Soc. Chim. Fr.* **1966**, 3878; c) F. G. Mann, F. H. Stewart, *J. Chem. Soc.* **1954**, 2826; d) T. Reichstein, J. Baud, *Helv. Chim. Acta* **1937**, *20*, 892; see also: e) M. I. Calaza, M. R. Paleo, F. J. Sardina, *J. Am. Chem. Soc.* **2001**, *123*, 2095; f) F. Foubelo, A. Gutierrez, M. Yus, *Synthesis* **1999**, 503; g) F. F. Fleming, B. C. Shook, *Tetrahedron Lett.* **2000**, *41*, 8847.
[88] V. A. Vu, L. Bérillon, P. Knochel, *Tetrahedron Lett.* **2001**, *42*, 6847.
[89] J. Thibonnet, V. A. Vu, L. Bérillon, P. Knochel, *Tetrahedron*, **2002**, *58*, 4787.
[90] R. H. Blaauw, J. C. J. Benningshof, A. E. Van Ginkel, J. H. van Maarseveen, H. Hiemstra, *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2250.
[91] J.-F. Brière, R. H. Blaauw, J. C. J. Benningshof, A. E. van Ginkel, J. H. van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.* **2001**, *12*, 2371.
[92] J. Thibonnet, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 3319.
[93] a) N. Krause, *Tetrahedron Lett.* **1989**, *30*, 5219; b) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 898.
[94] F. F. Fleming, V. Gudipati, O. W. Steward, *Org. Lett.* **2002**, *4*, 659.
[95] F. F. Fleming, Z. Zhang, Q. Wang, O. W. Steward, *Org. Lett.*, **2002**, *4*, 2493.
[96] A. Inoue, H. Shinokubo, K. Oshima, *Org. Lett.* **2000**, *2*, 651.
[97] V. A. Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 361; *Angew. Chem. Int. Ed.* **2002**, *41*, 351.
[98] a) C. Hamdouchi, C. Topolski, M. Goedken, H. M. Walborsky, *J. Org. Chem.* **1993**, *58*, 3148; b) G. Boche, D. R. Schneider, *Tetrahedron Lett.* **1978**, *19*, 2327; c) G. Boche, D. R. Schneider, H. Wintermayr, *J. Am. Chem. Soc.* **1980**, *102*, 5697.
[99] A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* **2000**, *100*, 93.
[100] a) O. R. Pierce, A. F. Meiners, E. T. McBee, *J. Am. Chem. Soc.* **1953**, *75*, 2516; b) C. N. Roberts, E. T. McBee, A. F. Meiners, *J. Am. Chem. Soc.* **1957**, *79*, 335; c) P. Moreau, R. Albachi, A. Commeyras, *Nouv. J. Chim.* **1977**, *1*, 497.
[101] a) S. Lavaire, R. Plantier-Royon, C. Portella, *Tetrahedron: Asymmetry* **1998**, *9*, 213; b) C. Portella, B. Dondy, *Tetrahedron Lett.* **1991**, *32*, 83.
[102] S. Avolio, C. Malan, I. Marek, P. Knochel, *Synlett* **1999**, 1820.
[103] a) Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, M. Koyama, *Tetrahedron* **1998**, *54*, 5557; b) R. W. Hoffmann, P. G. Nell, *Angew. Chem.* **1999**, *111*, 354; *Angew. Chem. Int. Ed.* **1999**, *38*, 338.
[104] A. E. Jensen, P. Knochel, *J. Organomet. Chem.* **2002**, *653*, 122.
[105] I. Sapountzis, P. Knochel, unpublished results.
[106] a) C. Amatore, A. Jutand, *J. Organomet. Chem.* **1999**, *576*, 254; b) J. F. Fauvarque, F. Pflüger, M. Troupel, *J. Organomet. Chem.* **1981**, *208*, 419.
[107] V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron Lett.* **2001**, *42*, 5717.
[108] V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429.
[109] K. S. Feldman, K. J. Eastman, G. Lessene, *Org. Lett.* **2002**, *4*, 3525.
[110] C. Dai, C. G. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719.
[111] a) R. Giovannini, P. Knochel, *J. Am. Chem. Soc.* **1998**, *120*, 11186; b) R. Giovannini, T. Stuedemann, A. Devesagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544.
[112] W. Dohle, D. M. Lindsay, P. Knochel, *Org. Lett.* **2001**, *3*, 2871.
[113] a) M. Tamaru, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487; b) M. Tamaru, J. K. Kochi, *Synthesis* **1971**, *93*, 303; c) M. Tamaru, J. K. Kochi, *J. Organomet. Chem.* **1971**, *31*, 289; d) M. Tamaru, J. K. Kochi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063; e) J. K. Kochi, *Acc. Chem. Res.* **1974**, *7*, 351; f) S. Neumann, J. K. Kochi, *J. Org. Chem.* **1975**, *40*, 599; g) R. S. Smith, J. K. Kochi, *J. Org. Chem.* **1976**, *41*, 502.
[114] a) G. Cahiez, S. Marquais, *Pure Appl. Chem.* **1996**, *68*, 53; b) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; c) G. Cahiez, H. Advedissian, *Synthesis* **1998**, 1199.
[115] a) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856; b) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed.* **2002**, *41*, 609.
[116] W. Dohle, F. Kopp, G. Cahiez, P. Knochel, *Synlett* **2001**, 1901.
[117] M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203.
[118] The halogen–copper exchange may have a high synthetic potential and offers a new entry to a range of new polyfunctionalized copper species: C. Piazza, P. Knochel, *Angew. Chem.* **2002**, *114*, 3397; *Angew. Chem. Int. Ed.* **2002**, *41*, 3267.

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Heterodimerization and cross-desensitization between the μ-opioid receptor and the chemokine CCR5 receptor

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Abstract

Cross-desensitization between μ-opioid receptor agonists and CC chemokines was shown to occur in immune cells and in the central nervous system. However, these cells do not permit examination of potential mechanisms at cellular levels due to low levels and mixed populations of receptors. In this study, we investigated possible interactions and biochemical mechanisms of cross-desensitization between the μ-opioid and chemokine CCR5 receptors coexpressed in Chinese hamster ovary (CHO) cells. Hemagglutinin (HA)-tagged μ-opioid receptor coimmunoprecipitated with FLAG (Asp–Tyr–Lys–Asp–Asp–Asp–Asp–Lys)-tagged chemokine receptor CCR5 in cells expressing the two receptors, but not in a mixture of cells transfected with one of the two receptors, indicating that the two receptors form heterodimers. Treatment with the μ-opioid receptor agonist DAMGO ([D-Ala^2, *N*-Me-Phe^4, Gly^5-ol]-enkephalin), the chemokine RANTES (Regulated on Activation, Normal T cell-Expressed and -Secreted) (CCL5), or both, did not affect the level of coimmunoprecipitation. DAMGO and RANTES (CCL5) induced chemotaxis in CHO cells coexpressing both receptors, and preincubation with either DAMGO or RANTES (CCL5) profoundly inhibited chemotaxis caused by the other. DAMGO pretreatment enhanced phosphorylation of the chemokine CCR5 receptor and reduced RANTES (CCL5)-promoted [^{35}S]GTPγS binding. Conversely, RANTES (CCL5) preincubation slightly increased phosphorylation of the μ-opioid receptor and significantly reduced DAMGO-induced [^{35}S]GTPγS binding. These results indicate that activation of either receptor affected G protein coupling of the other, likely due to enhanced phosphorylation of the receptor. Heterodimerization between the two receptors may contribute to the observed cross-desensitization.

Keywords: μ-Opioid receptor; CCR5 chemokine receptor; Heterodimer; Cross-desensitization

1. Introduction

Opiates and opioids interact with specific receptors to produce unique physiological and pharmacological effects, most notably modulation of pain perception and regulation of mood. The presence of at least three types of opioid receptors—μ, δ, and κ—was established in the 1970s and 1980s by pharmacological, binding, and anatomical distribution analyses. μ, δ, and κ opioid receptors have been cloned (for reviews, see Kieffer, 1995; Knapp et al., 1995). Activation of opioid receptors, coupled via pertussis toxin (PTX)-sensitive G proteins, induces a number of cellular effects, including inhibition of adenylyl cyclase, increase in K^+ conductance and decrease in Ca^{2+} conductance, and stimulation of the p42/p44 mitogen-activated protein (MAP) kinase pathways (for a review, see Law et al., 2000).

Exposure to opiates and opioids has been reported to inhibit cellular immune responses and induce chemotactic responses in immune cells (for reviews, see Peterson et al., 1998; McCarthy et al., 2001). These effects on the immune system may contribute to impaired immune function (Des Jarlais et al., 1988) and a higher rate of infection by the human immunodeficiency virus (HIV) in chronic heroin users (Holmberg, 1996). These effects are, at least in part, mediated by opioid receptors as the mRNAs of μ, δ, and κ opioid receptors have been shown to be present in immune cells (for a review, see McCarthy et al., 2001).

Chemokines and chemokine receptors play crucial roles in the functions of the immune system, including leukocyte

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development, and function and clearance of infectious organisms. Chemokine receptors CCR5 and CXCR4 act as major coreceptors, along with CD4, for the entry of HIV into cells (Cairns and D'Souza, 1998). In addition, recent studies have shown that chemokine and chemokine receptors are present in the central nervous system and play important roles in brain development, regulation of neurotransmission, and pathophysiological states in which inflammation persists (Bajetto et al., 2002). To date, 19 chemokine receptors have been identified, and many chemokines bind to multiple receptors and most chemokine receptors recognize several chemokines (for a review, see Proudfoot, 2002). Activation of chemokine receptors, coupled via G proteins ($G_{i/o}$, G_q, and G_{16}) (Arai and Charo, 1996), results in cellular effects such as inhibition of adenylyl cyclase (Zhao et al., 1998); stimulation of phospholipases A, C, and D; activation of p42/p44 MAP kinases; stimulation of phosphatidylinositol-3-kinase; and enhancement of nonreceptor tyrosine kinase activities (for reviews, see Bokoch, 1995; Maghazachi, 1999).

Opioid treatment of immune cells desensitized the chemotactic response induced by several chemokines; in turn, pretreatment with some chemokines reduced the chemotaxis induced by some opioids (Grimm et al., 1998a,b; Choi et al., 1999; Rogers et al., 2000; Miyagi et al., 2000). Heterologous desensitization of CCR5 may reduce susceptibility to HIV infection (Cairns and D'Souza, 1998; Shen et al., 2000; Szabo et al., in press). In addition, administration of some chemokines into the periaqueductal gray of the rat brain reduced the antinociceptive effects of μ-opioid receptor agonists (Szabo et al., 2002). Cross-talk between the opioid and chemokine systems may serve as a modulatory mechanism to fine-tune cellular function (for a review, see McCarthy et al., 2001).

Like many other G protein-coupled receptors (GPCRs), both the μ-opioid and chemokine CCR5 receptors are desensitized following prolonged agonist exposure (Zhang et al., 1996; Aramori et al., 1997). Two major types of desensitization have been characterized: homologous and heterologous. In homologous desensitization, only the activated receptor is desensitized, while in heterologous desensitization, activation of a receptor causes reduced responsiveness of another receptor. Homologous desensitization of GPCRs shares similar mechanisms; however, the mechanisms underlying heterologous desensitization of GPCRs are less uniform. Multiple processes may be involved in heterologous desensitization, including changes at the levels of receptors, G proteins, and second messenger pathways (Ali et al., 1999; Willars et al., 1999).

GPCRs have been shown to form dimers with the same receptor or a different receptor (for reviews, see Milligan, 2001; Devi, 2001; Angers et al., 2002). μ-Opioid receptors undergo heterodimerization with several GPCRs including the δ-opioid and β_2-adrenergic receptors. The ligand binding, signaling properties, and cellular function of a number of GPCRs have been reported to be modified as a result of receptor dimerization (for reviews, see Milligan, 2001; Devi, 2001; Angers et al., 2002).

In the present study, we investigated whether the μ-opioid and the chemokine CCR5 receptors formed heterodimers, and examined the early cellular signaling events following agonist binding, which may contribute to receptor cross-desensitization. We were not able to conduct such studies in immune cells and the central nervous system where cross-desensitization between opioids and chemokines has been reported, since these cells contain low levels of a heterogeneous population of opioid and chemokine receptors. The low levels of receptors do not permit biochemical characterization and the presence of several different chemokine and/or opioid receptors does not lend themselves to the unequivocal characterization of actions at a specific receptor type. We thus used a cell model, Chinese hamster ovary (CHO) cells stably coexpressing the CCR5 and μ-opioid receptors, for the study.

2. Materials and methods

2.1. Materials

[^{35}S]GTPγS (~1250 Ci/mmol), [^{3}H]diprenorphine (~58 Ci/mmol), and [^{32}P]orthophosphate (~8500 Ci/mmol) were purchased from Perkin Elmer Life Science (Boston, MA) and [^{125}I]MIP-1â was from Amersham Pharmacia Biotech (Piscataway, NJ). Naloxone was a gift from DuPont/Merck (Willmington, DE). Rabbit anti-FLAG polyclonal antibody (F-7425), Dulbecco's modified Eagle's medium, GDP, and GTPγS were obtained from Sigma (Louis, MO). The following reagents were purchased from the indicated companies: phospho-p44/42 MAPK antibody and HRP-conjugated antirabbit IgG (γ-immunoglobulin) from New England Biolaboratories (Beverly, MA); DAMGO from Research Biochemicals International (Natick, MA); human RANTES (CCL5) from PeproTech (Rocky Hill, NJ); 48-well microchemotaxis chamber from NeuroProbe (Gaithersburg, MD); Pansorbin from Calbiochem (San Diego, CA); geneticin from Mediatech (Herndon, VA); fetal calf serum from Hyclone (Logan, UT); Lipofectamine, hygromycin B, penicillin, streptomycin, and Hank's balanced salt solution from Invitrogen (Carlsbad, CA); Complete Mini Protease Inhibitor Cocktail Tablets™, M1, and M2 anti-FLAG monoclonal antibodies from Roche Diagnostics (Mannheim, Germany); SuperSignal chemiluminescent reagent from Pierce (Rockford, IL); PE-conjugated anti-CCR5 (2D7/CCR5) antibody from BD Pharmingen (San Diego, CA); mouse anti-hemagglutinin (HA) monoclonal antibody (HA.11), horseradish peroxidase-conjugated goat antimouse, and antirabbit IgG from Jackson ImmunoResearch Laboratory (West Grove, PA).

The human chemokine receptor CCR5 cDNA clone was obtained from the AIDS Research and Reference Reagent

Program, Division of AIDS, NIAID, NIH. The clone was originally donated by Dr. Nathaniel Landau of the Aron Diamond AIDS Research Center, The Rockefeller University. The CCR5 cDNA was epitope-tagged with FLAG at the N-terminus. The rat μ-opioid receptor cDNA clone (Chen et al., 1993) was a gift from Dr. Lei Yu of the University of Cincinnati and was tagged with HA at the N-terminus (Xu et al., 1999).

2.2. Coimmunoprecipitation of the μ-opioid and chemokine CCR5 receptors

CHO cells stably expressing HA-tagged rat μ-opioid receptor (HA-μ) (μ72) were transiently transfected with the FLAG-CCR5 (FLAG-tagged chemokine CCR5 receptor) cDNA with Lipofectamine. In parallel, CHO cells were similarly transfected with the FLAG-CCR5 cDNA. Forty-eight hours after transfection, cells transfected with both μ-opioid and chemokine CCR5 receptors (CHO-HA-μ/FLAG-CCR5) and a mixture of CHO-HA-μ and CHO-FLAG-CCR5 cells were harvested and solubilized in NIT solution (1.2% NP-40, 0.1 M iodoacetamide, 0.15 M NaCl, 20 mM Tris HCl, pH 7.4, and Complete Protease Inhibitor Cocktail™) for 1 h at 4 °C. The mixtures were centrifuged and filtered through 0.22-μM membranes, and the solubilized materials were incubated with rabbit polyclonal antibodies against FLAG (F7425) at 5 μg/ml for 1 h at 4 °C followed by Pansorbin (final 1/200) at 4 °C for 1 h. The mixture was centrifuged and the pellets were washed three times by centrifugation and resuspension. Immunoprecipitated materials were dissolved in Lammeli sample buffer containing 0.1 M DTT (dithiothreitol), subjected to 8% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (Chen et al., 1995), and transferred onto nitrocellulose membranes. Nitrocellulose membranes were treated with blocking solution and incubated with a monoclonal antibody against HA at 1:2000 dilution, and then goat antimouse IgG was conjugated with horseradish peroxidase at 1:4000 and reacted with chemiluminescence Western blotting detection reagents. The nitrocellulose membranes were then stripped and immunoblotting was carried out to assess the amount of FLAG-CCR5 immunoprecipitated with M1 mouse monoclonal antibodies against FLAG and goat antimouse IgG conjugated with horseradish peroxidase. In addition, Western blot was performed on the solubilized materials (without immunoprecipitation) with a monoclonal antibody against HA to assess the amounts of the HA rat μ-opioid receptor in the coexpressing cells and in the cell mixtures.

In a separate series of experiments, HA rat μ-opioid receptor was immunoprecipitated with rabbit antiserum against a C-terminal domain peptide (383–398) of the rat μ-opioid receptor (anti-RMOR) (1:500) (Chen et al., 1996) and immunoblotting was performed with M2 mouse monoclonal antibodies against FLAG (1:2000) according to the procedure described above.

2.3. Stable coexpression of the μ-opioid and FLAG-CCR5 receptors in CHO cells

CHO cell clones stably expressing the rat μ-opioid receptor in the vector pcDNA3/neomycin (Li et al., 1999) were transfected with the FLAG-CCR5 in the vector pcDNA3/hygromycin B using Lipofectamine. Forty-eight hours after transfection, cells were grown under the selection pressure of geneticin (1 mg/ml) and hygromycin (0.5 mg/ml) in DMEM/F12 (Dulbecco's modified Eagle's medium/F12 HAM) supplemented with 10% fetal calf serum in a humidified atmosphere with 5% CO_2 at 37 °C. Two weeks later, cells were transferred into 96-well plates at an average of 1 cell/well and, upon reaching confluence, clonal cells were transferred into 24-well plates in quadruplicate (three for experiments and one in a separate plate for propagation). Agonist-induced p42/p44 MAP kinase phosphorylation was used to screen for stable expression of both receptors. Briefly, when cells were about 80% confluent, the medium was aspirated and cells were washed, cultured in DMEM/F12 supplemented with 0.5% fetal calf serum, and incubated at 37 °C with 5% CO_2 for 2 h to reduce basal p42/p44 MAP kinase phosphorylation. DAMGO (10 μM), RANTES (CCL5) (10 nM), or medium was added to one well each and incubated for 10 min. The ligands were removed by aspiration and 2 × Laemmli sample buffer was added to the three wells [DAMGO, RANTES (CCL5), and blank], transferred to 1.5-ml Eppendorf tubes, and boiled immediately. Samples were analyzed by Western blot using phospho-p44/42 MAPK antibody according to the vendor's instructions (New England Biolaboratories). Clonal cells showing enhanced p44/42 MAP kinase phosphorylation by DAMGO and RANTES (CCL5) indicate coexpression of MOR and FLAG-CCR5, which was further confirmed by receptor binding with [^{3}H]diprenorphine and [^{125}I]macrophage inflammatory protein-1β (MIP-1β). Selected clonal cells were maintained in DMEM/F12 with 0.5 mg/ml geneticin and 0.2 mg/ml hygromycin. Cells were harvested for experiments by use of Versene solution (0.54 mM ethylenediaminetetraacetic acid, 0.14 mM NaCl, 2.7 mM KCl, 8.1 mM Na_2HPO_4, 1.46 mM KH_2PO_4, 1 mM glucose, pH 7.0).

2.4. Opioid receptor binding and internalization

Cell membranes were prepared as previously reported (Chen et al., 1996). Binding was carried out in 50 mM Tris–HCl buffer containing 1 mM EGTA (pH 7.4) at room temperature for 1 h in duplicate in a final volume of 1 ml with 10–20 μg of membrane protein. Saturation binding of [^{33}H]diprenorphine to the μ-opioid receptor was performed with at least six concentrations of [^{33}H]diprenorphine (ranging from 25 pM to 2 nM), and K_d and B_{max} values were determined. Competitive inhibition of [^{3}H]diprenorphine binding to the μ receptor was performed with 0.4 nM

[^{3}H]diprenorphine in the absence or presence of different concentrations of DAMGO, and K_i values of DAMGO were determined. Naloxone (1 μM) was used to define nonspecific binding. Binding data were analyzed with the EBDA program (McPherson, 1983).

For internalization studies, receptor binding was performed on intact cells with ~ 1 nM [^{3}H]diprenorphine in phosphate-buffered saline (PBS; pH 7.2). Nonspecific binding was defined with 1 μM naloxone for the total receptors and 5 μM CTAP (Cys^2, Tyr^3, Arg^5, and Pen^{7}Amide) for the cell surface receptors. The difference between the total receptors and the cell surface receptors represents intracellular receptors.

2.5. CCR5 binding

CCR5 binding assay was performed on intact cells according to a modification of the procedure described by Samson et al. (1996). Cells (7.5×10^4 cells/tube) were incubated with [^{125}I]MIP-1β (0.1 nM) and various concentrations of unlabeled MIP-1β (from 2 to 64 nM) at room temperature for 45 min, centrifuged at 4000 × *g* at 4 °C for 5 min, and washed two times by resuspension and centrifugation. Radioactivity associated with cells was measured in a gamma counter and binding data were analyzed with the EBDA program (McPherson, 1983).

2.6. Chemotaxis

The analysis of chemotaxis was performed by standard procedures (Grimm et al., 1998a) in a 48-well microchemotaxis chamber. Briefly, cells were incubated in RPMI-1640 medium containing 1% bovine serum albumin (BSA) and 25 mM HEPES in the upper chamber, and the chemoattractant was loaded in the bottom chamber in the same medium, separated by a polyvinylpyrrolidone-free 5-μm pore size membrane. Migration in response to DAMGO or RANTES (CCL5) was allowed for 90–180 min at 37 °C in 5% CO_2. The membranes were then removed from the chamber, the upper side was washed and scraped, and the membranes were fixed and stained. The results are expressed as the chemotaxis index (mean number of cells per high-power field for chemoattractant dilution/mean number of cells for the medium control).

2.7. [^{35}S]GTPγS binding

Cells were treated with or without the chemokine agonist RANTES (CCL5) or the μ-opioid receptor agonist DAMGO for an indicated period at 37 °C. Cells were then collected and membranes were prepared in the presence of 10 mM NaF and 10 mM Na pyrophosphate to inhibit phosphatases (Zhu et al., 1998). [^{35}S]GTPγS binding was performed as described previously (Li et al., 2001). Briefly, membranes (containing 10–20 μg of proteins) were incubated with 15 μM GDP and ~ 0.2 nM [^{35}S]GTPγS in the presence or absence of a drug in a reaction buffer (50 mM HEPES, 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, and 0.1% BSA) in a final volume of 0.5 ml. Nonspecific binding was determined in the presence of 10 μM GTPγS. After 60 min of incubation at 30 °C, bound and free [^{35}S]GTPγS were separated by filtration with GF/B filters under reduced pressure and the filter was washed. Radioactivity in filters was determined by liquid scintillation counting.

2.8. Phosphorylation of opioid and chemokine receptors

Phosphorylation of opioid and chemokine receptors was conducted according to a procedure described previously (Carman et al., 2000). CHO-MOR/FLAG-CCR5 cells were grown to confluence in six-well plates and two wells of cells were combined for each assay. Cells were washed twice with phosphate-free DMEM and incubated at 37 °C for 2 h with 1 ml/well phosphate-free DMEM containing 500 μCi/ml [^{32}P]orthophosphate. RANTES (CCL5) or DAMGO was then added and incubated for 10 min at 37 °C and washed three times with ice-cold PBS. All subsequent steps were carried out at 4 °C. Cells were solubilized for 2 h with 0.4 ml/well of solubilization buffer (2% digitonin, 0.5% sodium deoxycholate, 5 mM EDTA, 10 mM sodium pyrophosphate, 10 mM NaF, 20 nM calyclulin A, and 1 tablet/10 ml Complete Protease Inhibitor Cocktail™). Solubilized mixtures were centrifuged and the supernatants were precleared by incubation with Pansorbin and normal rabbit serum for 1 h. For immunoprecipitation of the opioid or chemokine receptors, the supernatant was incubated overnight with rabbit antiserum against a C-terminal domain peptide (383–398) of the rat μ-opioid receptor (2 μl for 0.8 ml) (Chen et al., 1996) and the rabbit anti-FLAG antibodies (4 μg for 0.8 ml), respectively, followed by Pansorbin (final 1/200) at 4°C for 1 h. The suspension was centrifuged at 9000 × *g* and the pellet was washed three times with solubilization solution by centrifugation and resuspension. The pellet was dissociated in 2 × Lammeli sample buffer and subjected to 7% SDS-PAGE and autoradiography.

2.9. Internalization of FLAG-CCR5

CHO-MOR/FLAG-CCR5 cells were harvested, washed, and resuspended in a medium containing RPMI-1640, 25 mM HEPES, glutamine, and 1% BSA. Cells were treated with 1 μM DAMGO or 12.5 nM RANTES (CCL5) and incubated for 30 min at 37 °C, washed with cold Hank's balanced salt solution with 2% endotoxin-free fetal calf serum, and resuspended in the same solution. Subsequently, cells were incubated with normal goat serum at 4 °C for 30 min to block nonspecific binding. Cells were treated with PE-conjugated anti-CCR5 (2D7/CCR5) antibody, incubated at 4 °C for 45 min, washed, and analyzed in a Coulter Epics XL flow cytometer (Coulter, Hialeah, FL).

3. Results

3.1. Heterodimerization of the μ-opioid receptor and the chemokine receptor CCR5

CHO-HA-μ cells expressed ~ 0.5 pmol/mg protein of HA-tagged μ-opioid receptor as determined by [^{3}H]diprenorphine binding. FLAG-CCR5 cDNA was transfected

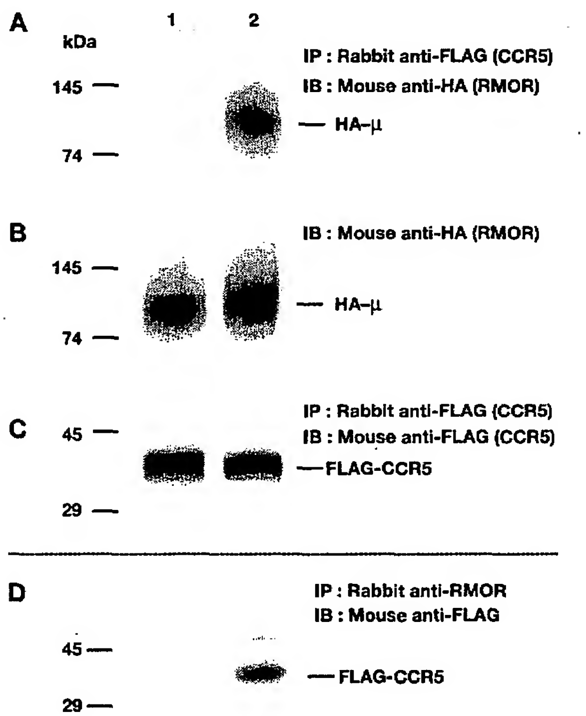

Fig. 1. Coimmunoprecipitation of the chemokine CCR5 receptor and the μ-opioid receptor in CHO cells cotransfected with both receptors. CHO cells or CHO cells stably expressing HA-μ were transiently transfected with the cDNA construct of the FLAG-CCR5 receptor. Forty-eight hours later, CHO-HA-μ/FLAG-CCR5 cells (lane 2) and a mixture of CHO-HA-μ and CHO-FLAG-CCR5 cells (Lane 1) were solubilized. (A) Solubilized materials were immunoprecipitated with rabbit anti-FLAG antibody (F7425) and Pansorbin. Immunoprecipitated materials were dissolved in Lammeli sample buffer containing 0.1 M DTT and resolved with SDS-PAGE; immunoblotting was performed with a monoclonal antibody against HA; and the goat antimouse IgG was conjugated with horseradish peroxidase and reacted with enhanced chemiluminescence detection reagents. (B) Solubilized materials were resolved with SDS-PAGE and immunoblotting was carried out with a monoclonal antibody against HA to detect the HA-μ-opioid receptor. Note that the levels of the μ receptor were similar in both lanes. (C) Membranes shown in (A) were stripped and reblotted with a monoclonal antibody against FLAG to detect immunoprecipitated FLAG-CCR5 receptor. Note that the levels of immunoprecipitated CCR5 receptor were similar in both lanes. (D) Solubilized materials were immunoprecipitated with rabbit anti-RMOR(383–398) and resolved on SDS-PAGE, and immunoblotting was carried out with M2 mouse monoclonal antibody against FLAG to detect FLAG-CCR5. The chemokine CCR5 receptor was detected in CHO-HA-μ/FLAG-CCR5 cells (lane 2), but not in the mixture of CHO cells expressing HA-μ or FLAG-CCR5 individually (lane 1). Each figure represents one of the three or four experiments performed with similar results.

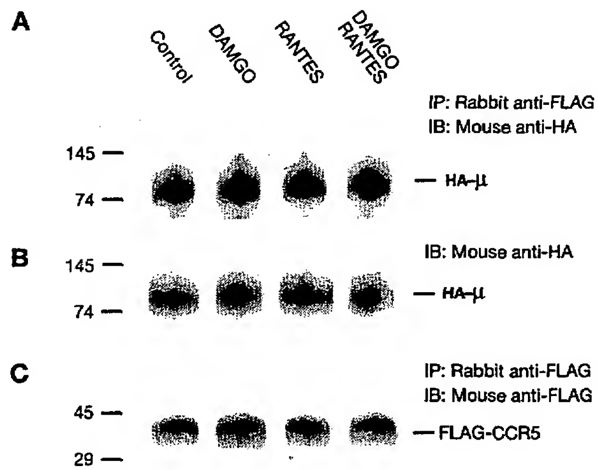

Fig. 2. Effects of agonist treatment on coimmunoprecipitation of the chemokine CCR5 receptor and the μ-opioid receptor. CHO cells stably transfected with HA-μ were transiently transfected with the cDNA construct of FLAG-CCR5. Forty-eight hours later, cells were left untreated or treated at 37 °C with DAMGO (1 μM), RANTES (CCL5) (12.5 nM or 100 ng/ml), or DAMGO (1 μM) and RANTES (CCL5) (12.5 nM) for 30 min, washed, detached with ice-cold Versene, and solubilized. (A–C) Solubilized materials were subjected to immunoprecipitation and immunoblotting as described in Fig. 1A–C. The figure represents one of the three experiments performed with similar results.

into CHO or CHO-HA-μ cells to approximately 1 pmol/10^6 cells. CHO-HA-μ/FLAG-CCR5 cells, or a mixture of CHO-HA-μ and CHO cells transfected with the FLAG-CCR5 receptor was solubilized and incubated with anti-FLAG antibody to immunoprecipitate FLAG-CCR5, and immunoprecipitated materials were resolved by SDS-PAGE followed by immunoblotting with anti-HA antibody to detect the HA-μ receptor. In cells coexpressing the HA-μ and FLAG-CCR5 receptors, the μ-opioid receptor coimmunoprecipitated with the chemokine receptor CCR5 (Fig. 1A), indicating formation of heterodimers or oligomers. In contrast, in a mixture of cells individually expressing HA-μ or FLAG-CCR5 receptors, the μ receptor was not coimmunoprecipitated with the CCR5 (Fig. 1A), even though the level of the μ-opioid receptor and the amount of immunoprecipitated CCR5 were similar (Fig. 1B and C). These results indicate that that the heterodimers were not formed during solubilization/immunoprecipitation procedures.

To confirm the finding, we carried out experiments using rabbit antiserum against a peptide of the C-terminal domain (383–398) of the rat μ-opioid receptor (Chen et al., 1996) to immunoprecipitate the μ-opioid receptor, followed by immunoblotting with a mouse monoclonal antibody against the FLAG epitope. In CHO cells expressing both HA-μ and FLAG-CCR5, there was a FLAG-immunoreactive protein band (Fig. 1D), indicating that FLAG-CCR5 immunoprecipitates with the μ-opioid receptor. In contrast, in mixtures of CHO cells expressing HA-μ or FLAG-CCR5 individually, there was no FLAG-immunoreactive band (Fig. 1D).

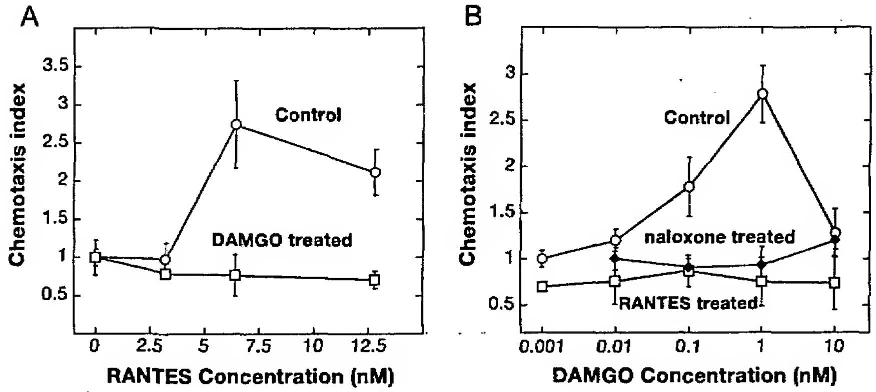

Fig. 3. Bidirectional cross-desensitization of the μ-opioid receptor and the chemokine receptor CCR5 in agonist-induced chemotaxis in CHO-MOR/FLAG-CCR5 cells. Cells were pretreated with either (A) DAMGO (10 nM) or (B) RANTES (CCL5) (100 ng/ml, 12.5 nM) or naloxone (1 μM) for 30 min. Migration of cells in response to (A) RANTES (CCL5) or (B) DAMGO was assayed as described in Materials and Methods. Results are expressed as chemotaxis index [mean number of cells per high-power field for DAMGO or RANTES (CCL5)/mean number of cells per high-power field for medium]. Each value represents the mean ± S.E.M. of three or four independent experiments performed in duplicate.

Treatment of CHO-HA-μ/FLAG-CCR5 cells with DAMGO, RANTES (CCL5), or both did not change the amount of the μ-opioid receptor coimmunoprecipitated with the chemokine CCR5 receptor (Fig. 2A). The level of the μ-opioid receptor and the amount of immunoprecipitated chemokine CCR5 receptor were similar in the control and treatment groups (Fig. 2B and C).

3.2. Establishment of CHO-MOR/FLAG-CCR5 cell lines

In our experience, stably transfected cell lines, but not transiently transfected cells, yielded consistent results for chemotactic responses, [^{35}S]GTPγS binding, and receptor phosphorylation. We thus established CHO-MOR/FLAG-CCR5 cell lines to assess the functional cross-desensitization between the chemokine receptor CCR5 and the μ-opioid receptor. Saturation binding with the radioligand [^{3}H]diprenorphine demonstrated a K_d value of 0.2 nM and a B_{max} value of 2.2 pmol/mg membrane protein for the rat μ-opioid receptor. In addition, saturation binding of the agonist [^{125}I]MIP-1β to the CCR5 in intact cells exhibited a K_d value of 13.1 nM and a B_{max} of 1.43 pmol/10^6 cells. No specific radioligand binding was detected in untransfected CHO cells and no ligand cross-reactivity could be detected in single-receptor transfected CHO cells (data not shown).

Table 1
Effect of DAMGO pretreatment on K_d and B_{max} values of [^{125}I]MIP-1β binding to CCR5 in CHO-MOR/FLAG-CCR5 cells

	K_d (nM)	B_{max} (pmol/10^6 cell)
Control	13.1 ± 1.47	1.43 ± 0.18
DAMGO-treated	11.9 ± 0.42	1.38 ± 0.11

Intact cells were preincubated with or without 1 μM DAMGO for 30 min at 37 °C. Binding was performed with 0.1 nM [^{125}I]MIP-1β and 2–64 nM MIP-1β (seven concentrations) at room temperature for 45 min, and K_d and B_{max} values were determined. Data are expressed as mean ± S.E.M. of three independent experiments performed in duplicate.

3.3. Chemotaxis

CHO-MOR/FLAG-CCR5 cells exhibited robust chemotactic responses to both RANTES (CCL5) and DAMGO (Fig. 3). CHO-MOR/FLAG-CCR5 cells failed to manifest a chemotactic response to DAMGO following pretreatment with the opioid receptor antagonist, naloxone (Fig. 3B), indicating that the chemotactic response to DAMGO is mediated by the μ-opioid receptor. In contrast, naloxone failed to alter the chemotactic response induced by RANTES (CCL5). CHO-MOR/FLAG-CCR5 cells pretreated with DAMGO failed to exhibit a chemotactic response to RANTES (CCL5) (Fig. 3A). Likewise, CHO-MOR/FLAG-CCR5 cells preincubated with RANTES (CCL5) failed to manifest a chemotactic response to DAMGO (Fig. 3B).

3.4. Receptor affinity and number

Next we examined whether changes in receptor affinity and number occurred during cross-desensitization. Pretreatment of CHO-MOR/FLAG-CCR5 cells with DAMGO did not affect the K_d and B_{max} values of [^{125}I]MIP-Iβ binding to CCR5 in intact cells (Table 1). In addition, RANTES (CCL5) pretreatment did not change significantly either

Table 2
Effect of RANTES (CCL5) pretreatment on K_i and B_{max} values of DAMGO in inhibiting [^{3}H]diprenorphine binding to the μ-opioid receptor in membranes

	K_i (nM)	B_{max} (pmol/mg protein)
Control	4.94 ± 1.38	2.20 ± 0.10
RANTES (CCL5)-treated	5.19 ± 1.26	2.27 ± 0.15

CHO-MOR/FLAG-CCR5 cells were pretreated with 6.25 nM (50 ng/ml) RANTES (CCL5) for 30 min at 37 °C and membranes were prepared. Competitive inhibition by DAMGO of [^{3}H]diprenorphine binding to the μ-opioid receptor was performed on membranes, and K_i and B_{max} values were calculated. Results are expressed as mean ± S.E.M. of four independent experiments performed in duplicate.

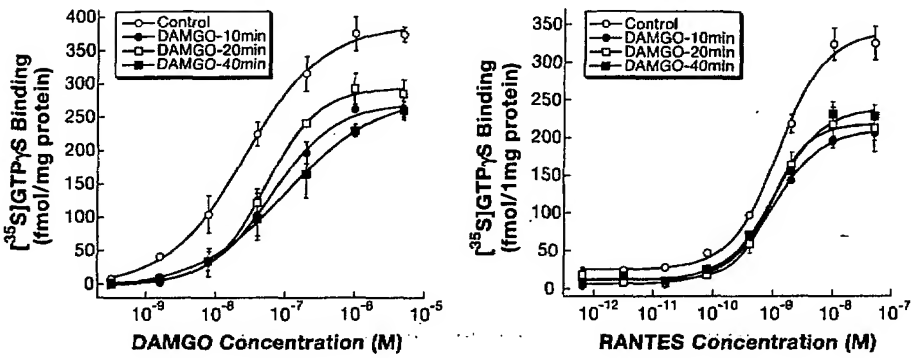

Fig. 4. Effects of DAMGO pretreatment on RANTES (CCL5)- and DAMGO-stimulated [^{35}S]GTPγS binding. CHO-MOR/FLAG-CCR5 cells were incubated without (control) or with 1 μM DAMGO for 10, 20, or 40 min at 37 °C. Cells were washed, membranes were prepared, and [^{35}S]GTPγS binding was performed in the presence of different concentrations of DAMGO or RANTES (CCL5) as described in Materials and Methods. Each value represents the mean ± S.E.M. of three or four independent experiments performed in duplicate. Basal [^{35}S]GTPγS binding (~ 150 fmol/mg protein) did not differ among the control and the treatment groups and was subtracted from the binding data. The EC_{50} and maximal levels of [^{35}S]GTPγS binding for RANTES (CCL5) and DAMGO are presented in Table 3.

the K_d or B_{max} of [^{3}H]diprenorphine binding to the μ-opioid receptor (data not shown), or the K_i or B_{max} values of DAMGO binding to the μ-opioid receptor in membranes (Table 2).

3.5. Receptor–G protein coupling

[^{35}S]GTPγS binding assay has been widely utilized to assess the agonist-dependent activation of PTX-sensitive G proteins mediated by a number of GPCRs including the μ-opioid and chemokine CCR5 receptors (Traynor and Nahorski, 1995; Zhao et al., 1998). We examined whether receptor–G protein coupling was affected during cross-desensitization. Both RANTES (CCL5) and DAMGO induced a dose-dependent increase in [^{35}S]GTPγS binding (Figs. 4 and 5), whereas no significant DAMGO- or RANTES (CCL5)-dependent effect upon [^{35}S]GTPγS binding was detected in untransfected CHO cells.

Pretreatment of CHO-MOR/FLAG-CCR5 cells with DAMGO reduced the maximal responses of RANTES (CCL5)- and DAMGO-promoted [^{35}S]GTPγS binding and increased the EC_{50} value of DAMGO, without affecting the EC_{50} value of RANTES (CCL5) (Fig. 4, Table 3). In contrast, pretreatment of cells expressing only FLAG-CCR5 with DAMGO did not affect the EC_{50} or B_{max} values of RANTES (CCL5) in enhancing [^{35}S]GTPγS binding (data not shown).

Preincubation with RANTES (CCL5) attenuated the maximal responses of RANTES (CCL5)- and DAMGO-promoted [^{35}S]GTPγS binding and increased the EC_{50} value of RANTES (CCL5), without affecting the EC_{50} value of DAMGO (Fig. 5, Table 4). Increasing pretreatment intervals (from 10 to 20 or 40 min) did not enhance the extent of desensitization (Figs. 4 and 5, Tables 3 and 4). However, preincubation of cells expressing the μ-opioid receptor alone with RANTES (CCL5) did not affect the EC_{50} or B_{max}

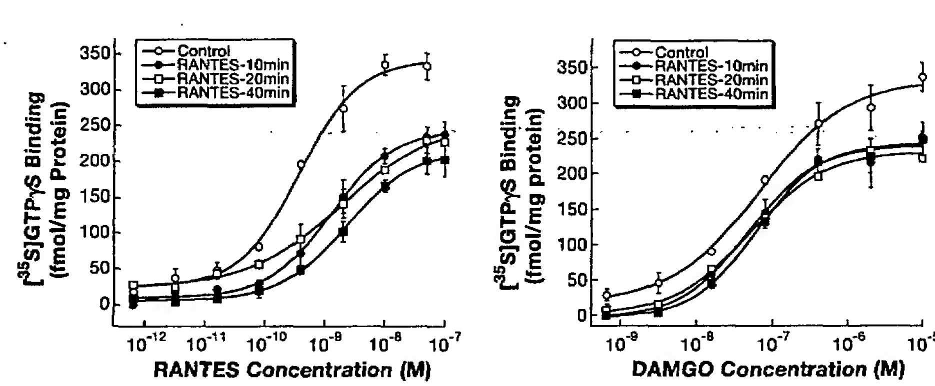

Fig. 5. Effects of RANTES (CCL5) pretreatment on DAMGO- and RANTES (CCL5)-promoted [^{35}S]GTPγS binding. CHO-MOR/FLAG-CCR5 cells were treated without (control) or with 6.25 nM (50 ng/ml) RANTES (CCL5) at 37 °C for 10, 20, or 40 min. Cells were washed, membranes were prepared, and [^{35}S]GTPγS binding was performed in the presence of different concentrations of DAMGO or RANTES (CCL5). Each value represents mean ± S.E.M. of three or four independent experiments in duplicate. Basal [^{35}S]GTPγS binding (~ 150 fmol/mg protein) did not differ among the control and the treatment groups, and was subtracted from the binding data. EC_{50} and maximal binding of [^{35}S]GTPγS binding induced by RANTES (CCL5) and DAMGO are shown in Table 4.

Table 3
EC_{50} and E_{max} values of RANTES (CCL5) and DAMGO in promoting [^{35}S]GTPγS binding following DAMGO pretreatment

DAMGO-pretreated	RANTES (CCL5)			DAMGO		
	EC_{50} (nM)	E_{max} (fmol/mg protein)	n	EC_{50} (nM)	E_{max} (fmol/mg protein)	n
Control	1.20 ± 0.22	323.0 ± 52.6	3	66.5 ± 12.1	329.0 ± 14.5	4
10 min	0.97 ± 0.05	198.7 ± 14.7	3	173.2 ± 23.1	230.3 ± 10.1	3
20 min	0.89 ± 0.12	189.3 ± 17.1	3	211.1 ± 38.2	253.8 ± 6.6	4
40 min	1.28 ± 0.11	190.7 ± 16.1	3	247.9 ± 18.9	240.3 ± 16.1	4

See Fig. 4 legend.

values of DAMGO in enhancing [^{35}S]GTPγS binding (data not shown).

These results indicate that pretreatment with either DAMGO or RANTES (CCL5) reduces the ability of the μ-opioid and chemokine CCR5 receptors to activate G proteins.

3.6. Receptor phosphorylation

Attenuation of receptor–G protein coupling may be due, in part, to receptor phosphorylation, which has been implicated in heterologous desensitization (Ali et al., 1999). We thus examined whether RANTES (CCL5) or DAMGO treatment could induce phosphorylation of the μ-opioid and/or chemokine CCR5 receptor(s). Preincubation with DAMGO, in addition to enhancing the phosphorylation of the μ-opioid receptor, significantly elevated phosphorylation of the CCR5 (Fig. 6). Likewise, RANTES (CCL5) pretreatment increased phosphorylation of both the CCR5 and the μ-opioid receptor (Fig. 6). However, the extent of phosphorylation of the μ-opioid and chemokine CCR5 receptors induced by RANTES (CCL5) and DAMGO, respectively, was less than those induced by the cognate agonists (Fig. 6). Molecular weight ranges of the μ-opioid and chemokine CCR5 receptors were similar to those previously reported (Chen et al., 1995; Zhang et al., 1996; El Kouhen et al., 1999; Oppermann et al., 1999; Carman et al., 2000).

3.7. Receptor internalization

Pretreatment with DAMGO for 30 min caused internalization of 25 ± 5% (mean ± S.E.M., n=4) of the μ

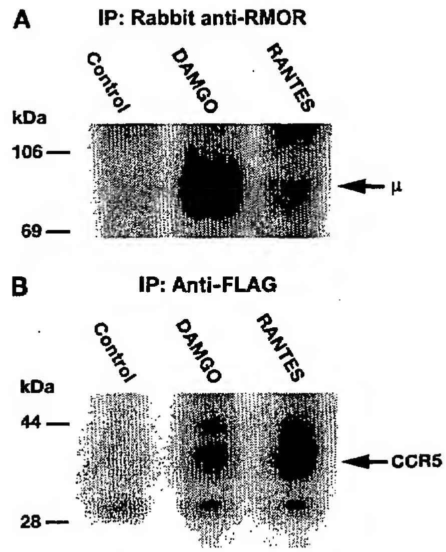

Fig. 6. Cross-phosphorylation of the μ-opioid and chemokine CCR5 receptors. CHO-MOR/FLAG-CCR5 cells were labeled with [^{32}P]phosphate and incubated with 1 μM DAMGO or 6.25 nM (50 ng/ml) RANTES (CCL5) at 37 °C for 10 min. Cells were lysed, solubilized, immunoprecipitated with (A) rabbit antiserum against a C-terminal domain peptide of the μ receptor or (B) rabbit polyclonal antibodies against the FLAG peptide, resolved by 10% SDS-PAGE, and subjected to autoradiography as described in Materials and Methods. The figures represent one of the five experiments performed with similar results. Longer incubation time up to 30 min yielded similar results.

receptor in MOR/FLAG-CCR5 cells and a similar extent in MOR cells as determined by receptor binding, but it did not affect the staining of FLAG-CCR5 on cell surface of cells expressing MOR/FLAG-CCR5 or FLAG-CCR5 alone by immunofluorescence flow cytometry. Etorphine, a nonselective opioid receptor agonist, yielded similar results (data now shown). In addition, following RANTES (CCL5) pretreatment, the numbers of total and cell surface μ-opioid receptors were unchanged in cells expressing MOR/FLAG-CCR5 or FLAG-MOR alone, whereas the same treatment induced significant internalization of FLAG-CCR5 in MOR/FLAG-CCR5 or FLAG-CCR5 cells. These results indicate that pretreatment with DAMGO does not alter internalization of the chemokine CCR5 receptor and ,likewise, RANTES (CCL5) preincubation does not affect internalization of the μ-opioid receptor.

Table 4
EC_{50} and E_{max} values of RANTES (CCL5) and DAMGO in promoting [^{35}S]GTPγS binding following RANTES (CCL5) pretreatment

RANTES (CCL5)-pretreated	DAMGO			RANTES (CCL5)		
	EC_{50} (nM)	E_{max} (fmol/mg protein)	n	EC_{50} (nM)	E_{max} (fmol/mg protein)	n
Control	47.8 ± 15.3	305.3 ± 9.8	4	0.72 ± 0.26	298.0 ± 25.9	4
10 min	54.3 ± 8.9	209.5 ± 11.6	4	4.40 ± 0.93	192.5 ± 15.2	4
20 min	46.0 ± 2.6	217.7 ± 19.2	3	7.86 ± 1.96	227.0 ± 14.5	3
40 min	55.3 ± 1.2	240.0 ± 9.5	3	9.30 ± 2.50	220.0 ± 10.2	3

See Fig. 5 legend.

4. Discussion

We have shown that the μ-opioid and chemokine CCR5 receptors coexpressed in CHO cells form heterodimers and cross-desensitize each other. Cross-desensitization is, at least in part, due to enhanced receptor phosphorylation and reduced receptor/G-protein. Heterodimerization of the two receptors may contribute to cross-desensitization.

4.1. Heterodimerization between the μ-opioid receptor and the chemokine receptor CCR5

The finding that HA-μ-opioid receptor and FLAG-CCR5 coimmunoprecipitated in cells coexpressing the two receptors, but not in a mixture of cells expressing individual receptors, demonstrates that the two receptors associate with each other when coexpressed. However, in Western blot analysis of immunoprecipitates, higher-molecular-weight species were not observed. In addition, phosphorylation studies revealed phosphorylated μ and chemokine CCR5 receptors at relative molecular weights similar to those reported previously for the individual receptors, but not any higher-molecular-weight bands. These results indicate that the interaction is sensitive to denaturing and/or reducing reagents, since the sample buffer for SDS-PAGE contains SDS and DTT, suggesting that interaction between the two receptors may involve noncovalent hydrophobic interactions and/or disulfide bond formation between the receptor proteins. Several dimerization interfaces have been proposed for GPCRs (Milligan, 2001; Devi, 2001; Angers et al., 2002); however, the actual mode of interactions between opioid and chemokine receptors requires further studies. Oligomerization of the μ-opioid receptor and CCR5 was reported in immune cells (Suzuki et al., 2002); however, the sharpness of the protein band and the molecular weight of the μ receptor differ from published reports (e.g., Zhang et al., 1996; El Kouhen et al., 1999). Different cell systems may play a role in the differences.

Agonist treatment had no effect on the level of heterodimerization between μ-opioid and chemokine CCR5 receptors as detected on Western blots (Fig. 2). Whether agonists affect homodimerization and heterodimerization of GPCRs depends on the receptor(s) involved (for reviews, see Milligan, 2001; Devi, 2001; Angers et al., 2002).

4.2. Chemotaxis

Although both DAMGO and RANTES (CCL5) induce chemotaxis, the concentration range in which RANTES (CCL5) is active is within a log unit, whereas that for DAMGO extends over three log units. The differences in the concentration ranges of an opioid vs. a chemokine that give a chemotactic response have been observed previously, and similar differences exist among the chemokines (e.g., Grimm et al., 1998a). For example, the chemotactic response of cells to CXCR4 ligands, such as stromal cell-derived factor-1α (CXCL12), occurs over a range of two to three orders of magnitude, while the optimal concentration of RANTES (CCL5) is much smaller. The capacity of chemoattractants to induce measurable chemotactic responses over different dose ranges is not understood. It may be due to differences in the relative capacity of these receptors to be desensitized. In those receptors that are particularly susceptible, this would result in reduced responsiveness or no responsiveness as the concentrations are increased. In addition, it is also possible that variability exists with respect to the specific G proteins that couple to a chemoattractant receptor (Arai and Charo, 1996). This may also contribute to the variability of responsiveness among GPCRs.

Our observation that the μ-opioid receptor agonist DAMGO promoted chemotaxis of CHO-MOR/FLAG-CCR5 cells is consistent with previous reports of opioids inducing chemotaxis in immune cells (Grimm et al., 1998a,b; Choi et al., 1999; Rogers et al., 2000; Miyagi et al., 2000). In addition, the findings that pretreatment with DAMGO reduced chemotaxis to RANTES (CCL5) and vice versa in CHO cells are in accord with previous studies in human peripheral blood monocytes and neutrophils and monkey leukocytes (Grimm et al., 1998a,b; Choi et al., 1999; Rogers et al., 2000; Miyagi et al., 2000). This indicates that CHO cells can be used as a model system to delineate possible mechanisms underlying cross-desensitization between these two receptors.

4.3. Receptor phosphorylation and receptor–G protein coupling

Pretreatment with DAMGO attenuated RANTES (CCL5)-induced [^{35}S]GTPγS binding; preincubation with RANTES (CCL5) likewise decreased DAMGO-promoted [^{35}S]GTPγS binding. Such a reduction in receptor–G protein coupling could be attributed to cross-phosphorylation of the μ-opioid and chemokine CCR5 receptors. Phosphorylation of unoccupied receptors by second messenger-dependent kinases activated by another receptor has been shown to contribute to cross-desensitization of chemoattractant GPCRs at the level of receptor–G protein coupling (for a review, see Ali et al., 1999). Zhang et al. (2003) recently showed that met-enkephalin inhibited both MIP-1α-mediated chemotaxis and Ca^{2+} flux of monocytes, and that Ca^{2+}-independent protein kinase C played an important role in heterologous desensitization.

DAMGO induced a more profound phosphorylation of the μ-opioid receptor than RANTES (CCL5), whereas RANTES (CCL5) increased phosphorylation of the CCR5 to a higher degree than DAMGO. This suggests that kinases involved in receptor phosphorylation and the residues phosphorylated in heterologous desensitization are likely to be different from those involved in homologous desensitization. GRK-mediated phosphorylation of agonist-occupied receptors has been shown to be involved in homologous desensitization of the μ-opioid receptor (Zhang et al., 1996) and the chemokine CCR5 receptor (Oppermann et al., 1999). The kinases contributing to the phosphorylation of the CCR5 and the μ-opioid receptor during cross-desensitization remain to be determined.

Differential receptor phosphorylation induced by DAMGO and RANTES (CCL5) may contribute to their differential effects upon the EC_{50} of the agonist-promoted [^{35}S]GTPγS binding in homologous and heterologous

desensitization. The EC_{50} value was increased only in homologous desensitization, but not in heterologous desensitization, although the E_{max} value was reduced in both. Consistent with this finding is the observation that pretreatment with DAMGO did not affect the affinity of RANTES (CCL5) for the CCR5, and incubation with RANTES (CCL5) did not change the affinity of DAMGO for the μ-opioid receptor. There are precedents in which receptor–G protein coupling is compromised with no changes in agonist affinity. For example, it was demonstrated that phosphorylation of the β_2-adrenoceptor by cAMP-dependent protein kinase, which induced heterologous desensitization, reduced receptor–G protein interaction, without affecting the binding affinity of isoproterenol to the receptor (Benovic et al., 1985). Since cAMP-dependent protein kinase phosphorylates the β_2-adrenoceptor at distinct sites from those for G protein-coupled receptor kinases (Lefkowitz et al., 1990), it is reasonable to assume that these differentially phosphorylated forms may adopt different conformations and hence exhibit different affinities for agonists. Whether this scheme is applicable to the cross-phosphorylated μ and CCR5 receptors requires further investigation. Our finding is different from a recent report by Zhang et al. (2003), who found that pretreatment of immune cells with met-enkephalin reduced the affinity of MIP-1α for the CCR1 receptor. Different chemokine receptors may be different.

Homologous desensitization and heterologous desensitization of the chemokine CCR5 receptor have differential impact on HIV entry. While homologous desensitization and internalization did not affect the activity of CCR5 as the HIV-1 coreceptor (Aramori et al., 1997), heterologous desensitization by activation of formyl peptide receptor or μ-opioid receptor impairs the HIV-1 coreceptor function of the chemokine CCR5 receptor (Shen et al., 2000; Szabo et al., in press).

Cross-phosphorylation of the receptors and reduction in receptor–G protein coupling may stem from heterodimerization of the receptors on the cell surface and sharing of common effector signal transducers such as G proteins. Both μ-opioid and chemokine CCR5 receptors have been reported to recruit PTX-sensitive G-proteins in CHO cells following agonist binding (Traynor and Nahorski, 1995; Zhao et al., 1998). However, it is not possible to define a causal relationship between heterodimerization and observed cross-desensitization as we have not found conditions that eliminate heterodimerization.

4.4. Homologous desensitization of the μ-opioid and chemokine CCR5 receptors

Following either DAMGO or RANTES (CCL5) treatment of CHO-MOR/FLAG-CCR5 cells, homologous desensitization was observed. This agrees with previous reports of homologous desensitization of the μ-opioid receptor (e.g., Zhang et al., 1996; El Kouhen et al., 1999) and the chemokine receptor CCR5 (Aramori et al., 1997; Zhao et al., 1998; Oppermann et al., 1999).

4.5. Discrepancy in the degree of cross-desensitization between chemotaxis and receptor–G protein coupling

Treatment of CHO-MOR/FLAG-CCR5 cells with RANTES (CCL5) abolished chemotactic response to DAMGO and vice versa. In contrast, preincubation with RANTES (CCL5) reduced the E_{max} value of DAMGO-promoted [^{35}S]GTPγS binding by ~30% without changing the EC_{50} value and vice versa. Thus, there is a difference in the degree of desensitization when chemotaxis and agonist-induced [^{35}S]GTPγS binding were used as the end points. The difference may be due to additional desensitization in the signal transduction pathway leading to chemotaxis, which requires further investigation.

The signal transduction pathways of GPCRs leading to chemotaxis have not been fully elucidated. Chemotaxis is a complex cellular response and may involve several different processes, such as cell polarization and shape change as well as cellular adhesion and migration (for a review, see Mellado et al., 2001). It was shown that stimulation of nonchemokine G_i-coupled receptors, but not G_s- or G_q-coupled receptors, promoted chemotaxis, and the release of free $G_{\beta\gamma}$ subunits of the G_i protein was required for chemotaxis (Neptune and Bourne, 1997; Arai et al., 1997). A number of cell type-dependent intracellular effectors such as arachidonic acid (Locati et al., 1994) and phosphatidylinositol 3-kinase (Haribabu et al., 1999) have been implicated, whereas others such as the p42/44 MAP kinase pathway and Ca^{2+} mobilization have been reported to be either necessary (Bacon et al., 1995; Groskopf et al., 1997) or not involved (Neptune and Bourne, 1997) in the regulation of cell migration via GPCRs. p38 MAP kinase activation and inhibition of adenylyl cyclase do not appear to be involved in chemokine-mediated chemotaxis (Neptune and Bourne, 1997).

RANTES (CCL5) and μ-opioid receptor agonists have been reported to induce tyrosine phosphorylation of the Src substrates p125FAK (focal adhesion kinase) and several cytoskeleton proteins (Bacon et al., 1996; Mangoura, 1997). Interaction of FAK with the cytoskeletal proteins, with their subsequent phosphorylation, has been reported to play a major role in cell polarization and migration (Clark and Brugge, 1995).

4.6. Receptor internalization

DAMGO caused internalization of the μ-opioid receptor but not CCR5; conversely, RANTES (CCL5) induced internalization of the CCR5, but not the μ-opioid receptor, in cells expressing both or alone. These findings suggested that the cross-desensitization between μ and CCR5 receptors may not be associated with receptor internalization in our system. These observations are similar to those of Szabo et

al. (in press), who found that activation of the μ-opioid receptor caused desensitization, but not internalization, of the chemokine CCR5 receptor in immune cells. Two possibilities may account for the lack of cointernalization of the two receptors. Although the receptors form heterodimers, they may be trafficked separately by the cell machinery. Heterodimers may dissociate before internalization and when some heterodimers are dissociated, others are formed as it is likely that there is an equilibrium between heterodimers and monomers of receptors. Another scenario is that since the percentage of receptors in heterodimers cannot be readily quantitated, the internalization results may be due primarily to the receptors not in heterodimers.

4.7. Concluding remarks

Cross-desensitization between the μ-opioid and chemokine CCR5 receptors, stably coexpressed in CHO cells, was demonstrated with both RANTES (CCL5) and DAMGO influencing in a reciprocal manner the chemotaxis, receptor phosphorylation, and $[^{35}S]GTP\gamma S$ binding of the other. Heterodimerization of the two receptors is likely to contribute to their cross-desensitization. Hence, our data suggest possible mechanisms for the inhibition of chemokine-induced directional migration of cells by which opiates and opioids may function in immunosuppression and inflammation, as well as for the desensitization of opioid-induced analgesia by RANTES (CCL5) administered into the periaqueductal gray. This cross-desensitization at the receptor and postreceptor levels may be utilized by the receptors to regulate the activity of the other and may contribute to alterations in intracellular effector pathways and subsequent impairment of immune function mediated by the other.

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References

Ali, H., Richardson, R.M., Haribabu, B., Snyderman, R., 1999. Chemoattractant receptor cross-desensitization [review]. J. Biol. Chem. 274, 6027–6030 (52 references).

Angers, S., Salahpour, A., Bouvier, M., 2002. Dimerization: an emerging concept for G protein-coupled receptor ontogeny and function. Annu. Rev. Pharmacol. Toxicol. 42, 409–435.

Arai, H., Charo, I.F., 1996. Differential regulation of G-protein-mediated signaling by chemokine receptors. J. Biol. Chem. 271, 21814–21819.

Arai, H., Tsou, C.L., Charo, I.F., 1997. Chemotaxis in a lymphocyte cell line transfected with C-C chemokine receptor 2B: evidence that directed migration is mediated by betagamma dimers released by activation of Galphai-coupled receptors. Proc. Natl. Acad. Sci. U. S. A. 94, 14495–14499.

Aramori, I., Ferguson, S.S., Bieniasz, P.D., Zhang, J., Cullen, B., Cullen, M.G., 1997. Molecular mechanism of desensitization of the chemokine receptor CCR-5: receptor signaling and internalization are dissociable from its role as an HIV-1 co-receptor. EMBO J. 16, 4606–4616 (published erratum appears in EMBO J. Oct. 1, 16 (19), 6055, 1997).

Bacon, K.B., Premack, B.A., Gardner, P., Schall, T.J., 1995. Activation of dual T cell signaling pathways by the chemokine RANTES. Science 269, 1727–1730.

Bacon, K.B., Szabo, M.C., Yssel, H., Bolen, J.B., Schall, T.J., 1996. RANTES induces tyrosine kinase activity of stably complexed p125FAK and ZAP-70 in human T cells. J. Exp. Med. 184, 873–882.

Bajetto, A., Bonavia, R., Barbero, S., Schettini, G., 2002. Characterization of chemokines and their receptors in the central nervous system: physiopathological implications. J. Neurochem. 82, 1311–1329.

Benovic, J.L., Pike, L.J., Cerione, R.A., Staniszewski, C., Yoshimasa, T., Codina, J., Caron, M.G., Lefkowitz, R.J., 1985. Phosphorylation of the mammalian beta-adrenergic receptor by cyclic AMP-dependent protein kinase. Regulation of the rate of receptor phosphorylation and dephosphorylation by agonist occupancy and effects on coupling of the receptor to the stimulatory guanine nucleotide regulatory protein. J. Biol. Chem. 260, 7094–7101.

Bokoch, G.M., 1995. Chemoattractant signaling and leukocyte activation [review]. Blood 86, 1649–1660 (171 references).

Cairns, J.S., D'Souza, M.P., 1998. Chemokines and HIV-1 second receptors: the therapeutic connection [review]. Nat. Med. 4, 563–568 (76 references).

Carman, C.V., Barak, L.S., Chen, C., Liu-Chen, L.-Y., Onorato, J.J., Kennedy, S.P., Caron, M.G., Benovic, J.L., 2000. Mutational analysis of G beta gamma and phospholipid interaction with G protein-coupled receptor kinase 2. J. Biol. Chem. 275, 10443–10452.

Chen, Y., Mestek, A., Liu, J., Hurley, J.A., Yu, L., 1993. Molecular cloning and functional expression of a μ-opioid receptor from rat brain. Mol. Pharmacol. 44, 8–12.

Chen, C., Xue, J.C., Zhu, J., Chen, Y.W., Kunapuli, S., Kim, D.R., Yu, L., Liu-Chen, L.-Y., 1995. Characterization of irreversible binding of beta-funaltrexamine to the cloned rat mu opioid receptor. J. Biol. Chem. 270, 17866–17870.

Chen, C., Yin, J., Riel, J.K., DesJarlais, R.L., Raveglia, L.F., Zhu, J., Liu-Chen, L.-Y., 1996. Determination of the amino acid residue involved in $[^3H]$beta-funaltrexamine covalent binding in the cloned rat mu-opioid receptor. J. Biol. Chem. 271, 21422–21429.

Choi, Y., Chuang, L.F., Lam, K.M., Kung, H.F., Wang, J.M., Osburn, B.I., Chuang, R.Y., 1999. Inhibition of chemokine-induced chemotaxis of monkey leukocytes by mu-opioid receptor agonists. In Vivo 13, 389–396.

Clark, E.A., Brugge, J.S., 1995. Integrins and signal transduction pathways: the road taken. Science 268, 233–239.

Des Jarlais, D.C., Friedman, S.R., Stoneburner, R.L., 1988. HIV infection and intravenous drug use: critical issues in transmission dynamics, infection outcomes, and prevention. Rev. Infect. Dis. 10, 151–158.

Devi, L.A., 2001. Heterodimerization of G-protein-coupled receptors: pharmacology, signaling and trafficking. Trends Pharmacol. Sci. 22, 532–537.

El Kouhen, R., Kouhen, O.M., Law, P.Y., Loh, H.H., 1999. The absence of a direct correlation between the loss of [D-Ala^2, MePhe^4,Gly^5-ol]enkephalin inhibition of adenylyl cyclase activity and agonist-induced mu-opioid receptor phosphorylation. J. Biol. Chem. 274, 9207–9215.

Grimm, M.C., Ben-Baruch, A., Taub, D.D., Howard, O.M., Resau, J.H., Wang, J.M., Ali, H., Richardson, R., Snyderman, R., Oppenheim, J.J., 1998a. Opiates transdeactivate chemokine receptors: delta and mu opiate receptor-mediated heterologous desensitization. J. Exp. Med. 188, 317–325.

Grimm, M.C., Ben-Baruch, A., Taub, D.D., Howard, O.M., Wang, J.M., Oppenheim, J.J., 1998b. Opiate inhibition of chemokine-induced chemotaxis [review]. Ann. N.Y. Acad. Sci. 840, 9–20 (32 references).

Groskopf, J.C., Syu, L.J., Saltiel, A.R., Linzer, D.I., 1997. Proliferin induces endothelial cell chemotaxis through a G protein-coupled, mito-

gen-activated protein kinase-dependent pathway. Endocrinology 138, 2835–2840.

Haribabu, B., Zhelev, D.V., Pridgen, B.C., Richardson, R.M., Ali, H., Snyderman, R., 1999. Chemoattractant receptors activate distinct pathways for chemotaxis and secretion. Role of G-protein usage. J. Biol. Chem. 274, 37087–37092.

Holmberg, S.D., 1996. The estimated prevalence and incidence of HIV in 96 large US metropolitan areas. Am. J. Public Health 86, 642–654.

Kieffer, B.L., 1995. Recent advances in molecular recognition and signal transduction of active peptides: receptors for opioid peptides [review]. Cell. Mol. Neurobiol. 15, 615–635.

Knapp, R.J., Malatynska, E., Collins, N., Fang, L., Wang, J.Y., Hruby, V.J., Roeske, W.R., Yamamura, H.I., 1995. Molecular biology and pharmacology of cloned opioid receptors [review]. FASEB J. 9, 516–525.

Law, P.-Y., Wong, Y.H., Loh, H.H., 2000. Molecular mechanisms and regulation of opioid receptor signaling. Annu. Rev. Pharmacol. Toxicol. 40, 389–430.

Lefkowitz, R.J., Hausdorff, W.P., Caron, M.G., 1990. Role of phosphorylation in desensitization of the β-adrenoceptor. Trends Pharmacol. Sci. 11, 190–194.

Li, J.G., Chen, C., Luo, L.-Y., Yin, J., Rice, K., Zhang, Y., Matecka, D., de Riel, J.K., DesJarlais, R.L., Liu-Chen, L.-Y., 1999. Asp147 in the third transmembrane helix of the rat μ opioid receptor forms ion-pairing with morphine and naltrexone. Life Sci. 65, 175–185.

Li, J., Huang, P., Chen, C., de Riel, J.K., Weinstein, H., Liu-Chen, L.-Y., 2001. Constitutive activation of the mu opioid receptor by mutation of D3.49(164), but not D3.32(147): D3.49(164) is critical for stabilization of the inactive form of the receptor and for its expression. Biochemistry 40, 12039–12050.

Locati, M., Zhou, D., Luini, W., Evangelista, V., Mantovani, A., Sozzani, S., 1994. Rapid induction of arachidonic acid release by monocyte chemotactic protein-1 and related chemokines. Role of Ca^{2+} influx, synergism with platelet-activating factor and significance for chemotaxis. J. Biol. Chem. 269, 4746–4753.

Maghazachi, A.A., 1999. Intracellular signalling pathways induced by chemokines in natural killer cells [review]. Cell Signal. 11, 385–390 (63 references).

Mangoura, D., 1997. mu-Opioids activate tyrosine kinase focal adhesion kinase and regulate cortical cytoskeleton proteins cortactin and vinculin in chick embryonic neurons. J. Neurosci. Res. 50, 391–401.

McCarthy, L., Wetzel, M., Sliker, J.K., Eisenstein, T.K., Rogers, T.J., 2001. Opioids, opioid receptors, and the immune response. Drug Alcohol Depend. 62, 111–123.

McPherson, G.A., 1983. A practical computer based approach to the analysis of radioligand binding experiments. Comput. Prog. Biomed. 17, 107–114.

Mellado, M., Rodriguez-Frade, J.M., Manes, S., Martinez, A., 2001. Chemokine signaling and functional responses: the role of receptor dimerization and tk pathway activation. Annu. Rev. Immunol. 19, 397–421.

Milligan, G., 2001. Oligomerisation of G-protein-coupled receptors. J. Cell Sci. 114, 1265–1271.

Miyagi, T., Chuang, L.F., Lam, K.M., Kung, H., Wang, J.M., Osburn, B.I., Chuang, R.Y., 2000. Opioids suppress chemokine-mediated migration of monkey neutrophils and monocytes—an instant response. Immunopharmacology 47, 53–62.

Neptune, E.R., Bourne, H.R., 1997. Receptors induce chemotaxis by releasing the betagamma subunit of Gi, not by activating Gq or Gs. Proc. Natl. Acad. Sci. U. S. A. 94, 14489–14494.

Oppermann, M., Mack, M., Proudfoot, A.E., Olbrich, H., 1999. Differential effects of CC chemokines on CC chemokine receptor 5 (CCR5) phosphorylation and identification of phosphorylation sites on the CCR5 carboxyl terminus. J. Biol. Chem. 274, 8875–8885.

Peterson, P.K., Molitor, T.W., Chao, C.C., 1998. The opioid–cytokine connection [review]. J. Neuroimmunol. 83, 63–69 (65 references).

Proudfoot, A.E., 2002. Chemokine receptors: multifaceted therapeutic targets. Nat. Rev. Immunol. 2, 106–115.

Rogers, T.J., Steele, A.D., Howard, O.M.Z., Oppenheim, J.J., 2000. Bidirectional heterologous desensitization of opioid and chemokine receptors. Ann. N.Y. Acad. Sci. 918, 19–28.

Samson, M., Labbe, O., Mollereau, C., Vassart, G., Parmentier, M., 1996. Molecular cloning and functional expression of a new human CC-chemokine receptor gene. Biochemistry 35, 3362–3367.

Shen, W., Li, B., Wetzel, M.A., Rogers, T.J., Henderson, E.E., Su, S.B., Gong, W., Le, Y., Sargeant, R., Dimitrov, D.S., Oppenheim, J.J., Wang, J.M., 2000. Down-regulation of the chemokine receptor CCR5 by activation of chemotactic formyl peptide receptor in human monocytes. Blood 96, 2887–2894.

Suzuki, S., Chuang, L.F., Yau, P., Doi, R.H., Chuang, R.Y., 2002. Interactions of opioid and chemokine receptors: oligomerization of mu, kappa, and delta with CCR5 on immune cells. Exp. Cell Res. 280, 192–200.

Szabo, I., Chen, X.H., Xin, L., Adler, M.W., Howard, O.M., Oppenheim, J.J., Rogers, T.J., 2002. Heterologous desensitization of opioid receptors by chemokines inhibits chemotaxis and enhances the perception of pain. Proc. Natl. Acad. Sci. U. S. A. 99, 10276–10281.

Szabo, I., Wetzel, M.A., Zhang, N., Steele, A.D., Kaminsky, D.E., Chen, L.Y., Liu-Chen, L.Y., Bednar, F., Henderson, E.E., Howard, O.M., Oppenheim, J.J., Rogers, T.J., 2003. Selective inactivation of CCR5 and decreased infectivity of R5 HIV-1 strains mediated by opioid-induced heterologous desensitization. J. Leukoc. Biol. (in press).

Traynor, J.R., Nahorski, S.R., 1995. Modulation by mu-opioid agonists of guanosine-5′-O-(3-[^{35}S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. Mol. Pharmacol. 47, 848–854.

Willars, G.B., Muller-Esterl, W., Nahorski, S.R., 1999. Receptor phosphorylation does not mediate cross talk between muscarinic M(3) and bradykinin B(2) receptors. Am. J. Physiol. 277, C859–C869 (see comments).

Xu, W., Ozdener, F., Li, J.G., Chen, C., de Riel, J.K., Weinstein, H., Liu-Chen, L.-Y., 1999. Functional role of the spatial proximity of Asp114(2.50) in TMH 2 and Asn332(7.49) in TMH 7 of the mu opioid receptor. FEBS Lett. 447, 318–324.

Zhang, L., Yu, Y., Mackin, S., Weight, F.F., Uhl, G.R., Wang, J.B., 1996. Differential mu opiate receptor phosphorylation and desensitization induced by agonists and phorbol esters. J. Biol. Chem. 271, 11449–11454.

Zhang, N., Hodge, D., Rogers, T.J., Oppenheim, J.J., 2003. Ca^{2+}-independent protein kinase Cs mediate heterologous desensitization of leukocyte chemokine receptors by opioid receptors. J. Biol. Chem. 278, 12729–12736.

Zhao, J., Ma, L., Wu, Y.L., Wang, P., Hu, W., Pei, G., 1998. Chemokine receptor CCR5 functionally couples to inhibitory G proteins and undergoes desensitization. J. Cell. Biochem. 71, 36–45.

Zhu, J., Luo, L.Y., Mao, G.F., Ashby, B., Liu-Chen, L.-Y., 1998. Agonist-induced desensitization and down-regulation of the human kappa opioid receptor expressed in CHO cells. J. Pharmacol. Exp. Ther. 285, 28–36.

TABLE 2. Chemokine receptor antagonists reported to be in clinical development

Target	Compound name and company	Development status	Disease
CCR1	BX-471 (ZK-811752) (Berlex Biosciences/Schering AG)	Phase II	MS, Pso, eczema
	BX-471 (ZK-811752) (Berlex Biosciences/Schering AG)	Phase I	Alzheimer disease
	MLN-3897 (Millennium Pharmaceuticals/ Aventis)	Phase II	RA, MS, Pso
	MLN-3701 (Millennium Pharmaceuticals)	Phase I	RA
CCR2	MLN-1202 (antibody) (Millenium Pharmaceuticals)	Phase II	RA
	Unknown (Incyte Pharmaceuticals)	Phase I	RA
CCR3	CAT-213 (antibody, bertilimumab) (Cambridge AT)	Phase II	Rhinitis, conjunctivitis
	GW-766994 (GlaxoSmithKline)	Phase II	Asthma, allergic rhinitis
	DPC-168 (Bristol-Myers Squibb)	Phase I	Asthma
CCR5	UK-427857 (Pfizer)	Phase II	HIV infection,
	ONO-4128 (Ono Pharmaceutical /GlaxoSmith-Kline)	Phase II	HIV infection
	Sch-351125/Sch-417690 (Schering-Plough)	Phase I	HIV infection
CXCR1/2	SB-332235 (GlaxoSmithKline)	Phase I	COPD, RA, Pso
CXCR4	AMD-3100 (AnorMED)	Phase II Phase I	Stem cell transplantation Repair of cardiac tissue after heart attack
	AMD-070 (AnorMED)	Phase I	HIV infection
	CTCE-0214 (Chemokine Therapeutics)	Phase II	Stem cell transplantation

NOTE: Data from Refs. 12 and 44–46.
ABBREVIATIONS: COPD, chronic obstructive pulmonary disease; MS, multiple sclerosis; Pso, psoriasis; RA, rheumatoid arthritis.

CCR1

The most advanced CCR1 antagonist in development is apparently compound BX-741, also named ZK-811752 (Banyu/Schering). It is a potent and selective

antagonist of the human receptor[34,47] but 100–200 times less potent against the rat and the mouse receptor. However, the compound has proven to be effective in several animal models when administered at high doses.[34,47] The phase I studies gave positive results, and phase II trials for multiple sclerosis patients were reported to be planned for March 2002.[47] A total of 94 patients were supposed to be treated three times a day for 16 weeks, but results from this trial have not been released yet. The compound is also in development for psoriasis and Alzheimer disease.

The compound CP-481,715, a potent human CCR1 antagonist (Pfizer) provided the first proof of concept for a chemokine receptor antagonist in RA.[48] In this trial, 12 patients received 300 mg of the compound every 8 h and 4 patients received placebo by oral route for 15 days. Biopsy specimens taken on days 1 and 15 showed that patients treated with the compound had a reduced number of $CCR1^+$ cells in their joints. A trend toward a clinical improvement was also observed.[48] The compound progressed into a 6-week phase II clinical trial, and development was canceled.[45]

Millenium Pharmaceuticals recently reported the completion of phase I with its candidate, MLN-3897, a CCR1 antagonist. Another candidate targeting the same receptor is MLN3701, which has recently advanced to a phase I trial.

CCR2

Incyte Pharmaceuticals has a small-molecule CCR2 antagonist in phase I trials for RA. Millennium Pharmaceuticals is developing an anti-CCR2 antibody (MLN-1202), which is currently in phase II for the same indication. It will be interesting to know whether CCR2 blockade shows a beneficial effect on patients with RA, given the results obtained with CCR2 knockout mice.[41]

CXCR3

Compound T0906487 (originally from Tularik) was being developed by Amgen and Chemocentryx. The compound was evaluated in a phase IIa clinical trial in 40 patients with moderate to severe psoriasis who received 50 and 200 mg of the compound once a day for 28 days. Results indicated that the treatment had no effect on the psoriatic area severity index (PASI) or on the patient's global assessment (PGA) scores. The development of the compound for psoriasis was canceled.[49] The compound was also in development for RA, but no results for this disease have been reported yet.

CONCLUSIONS

The discovery of chemokines exerted a profound effect on our understanding of cell trafficking in health and disease. The potential of chemokines as therapeutic targets soon become evident, but initial optimism has been moderated by failures of compounds in the clinic. In the future, chemokine receptor antagonists will compete with other agents currently in development that also target cell migration. Time will tell whether chemokines are useful therapeutic targets or just a fascinating family of mediators.

[NOTE ADDED IN PROOF:] After less than four months on the market, Tysabri was withdrawn because one person died and another one contracted a rare disease of the cental nervous system called "progressive multifocal leukoencephalopathy." It is believed that both cases were caused by adverse side effects from the combination therapy of Tyrsabri and Avonex (interferon). Source: Press Release. Available at: <http://ms.about.com/b/a/150342.htm>

REFERENCES

1. LUSTER, A.D. 1998. Chemokines-chemotactic cytokines that mediate inflammation. N. Engl. J. Med. **338:** 436–445.
2. ZLOTNIK, A. & O. YOSHIE. 2000. Chemokines: a new classification system and their role in immunity. Immunity **12:** 121–127.
3. GERARD, C. & B.J. ROLLINS. 2001. Chemokines and disease. Nat. Immunol. **2:** 108–115.
4. GODESSART, N. & S.L. KUNKEL. 2001. Chemokine in autoimmune disease. Curr. Opin. Immunol. **13:** 670–675.
5. MURPHY, P.M., *et al.* 2000. International Union of Pharmacology. XXII. Nomenclature for chemokine receptors. Pharmacol. Rev. **52:** 145–176.
6. ONUFFER, J. & R. HORUCK. 2002. Chemokines, chemokine receptors and small-molecule antagonists: recent developments. Trends Pharm. Sci. **23:** 459–467.
7. JOHNSON, Z. *et al.* 2004. Chemokine inhibition—why, when where, which and how? Biochem. Soc. Trans. **32:** 366–377.
8. MOSER, B. *et al.* 2004. Chemokines: multiple levels of leukocyte migration control. Trends Immunol. **25:** 75–84.
9. BARDI, G. *et al.* 2001. The T cell chemokine receptor CCR7 is internalized on stimulation with ELC, but not with SLC. Eur. J. Immunol. **31:** 3291–3297.
10. KOHOUT, T.A. *et al.* 2004. Differential desensitization, receptor phosphorylation, beta-arrestin recruitment, and ERK1/2 activation by the two endogenous ligands for the CC chemokine receptor 7. J. Biol Chem. **279:** 23214–23222.
11. MARIANI, M. *et al.* 2004. Dominance of CCL22 over CCL17 in induction of chemokine receptor CCR4 desensitization and internalization on human Th2 cells. Eur. J. Immunol. **34:** 231–240.
12. TERRICABRAS, E., C. BENJAMIN & N. GODESSART. 2004. Drug discovery and chemokine receptor antagonists: eppur si muove! Autoimmunity Rev. **3:** 550–556.
13. PETKOVIC, V. *et al.* 2004. Eotaxin-3/CCL26 is a natural antagonist for CC chemokine receptors 1 and 5. A human chemokine with a regulatory role. J. Biol. Chem. **279:** 23357–23363.
14. OGILVIE, P. *et al.* 2003. Eotaxin-3 is a natural antagonist for CCR2 and exerts a repulsive effect on human monocytes. Blood **102:** 789–794.
15. OGILVIE, P. *et al.* 2004. Unusual chemokine receptor antagonism involving a mitogen-activated protein kinase pathway. J. Immunol. **172:** 6715–6722
16. LOETSCHER, P. *et al.* 2001. The ligands of CXC chemokine receptor 3, I-TAC, Mig, and IP10, are natural antagonists for CCR3. J. Biol. Chem. **276:** 2986–2991.
17. XANTHOU, G. *et al.* 2003. CCR3 functional responses are regulated by both CXCR3 and its ligands CXCL9, CXCL10 and CXCL11. Eur. J. Immunol. **33:** 2241–2250.
18. PETKOVIC, V. *et al.* 2004. I-TAC/CXCL11 is a natural antagonist for CCR5. J. Leukoc. Biol. **76:** 701–708.
19. LASAGNI, L. *et al.* 2003. An alternatively spliced variant of CXCR3 mediates the inhibition of endothelial cell growth induced by IP-10, Mig, and I-TAC, and acts as functional receptor for platelet factor 4. J. Exp. Med. **197:** 1537–1549.
20. FULKERSON, P.C. *et al.* 2004. Negative regulation of eosinophil recruitment to the lung by the chemokine monokine induced by IFN-gamma (Mig, CXCL9). Proc. Natl. Acad. Sci. USA **101:** 1987–1992.
21. THOMAS, M.S. *et al.* 2004. Regulation of cockroach antigen-induced allergic airway hyperreactivity. J. Immunol. **173:** 615–623.

22. MIYASAKA, M. & T. TANAKA. 2004. T lymphocyte trafficking across high endothelial venules: dogmas end enigmas. Nat. Rev. Immunol. **4:** 360–370.
23. IMHOF, B.A. & M. AURRAND-LIONS. 2004. Adhesion mechanisms regulating the migration of monocytes. Nat. Rev. Immunol. **4:** 432–444.
24. O'CONNOR, P.W. *et al.* 2004. Natalizumab Multiple Sclerosis Trial Group. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology **62:** 2038–2043.
25. SANDBORN, W. *et al.* 2004. A phase III, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of antegren (Natalizumab) in maintaining clinical response and remission in Crohn's disease (ENACT-2). Gastroenterology **127:** 332–339.
26. LEBWOHL, M. *et al.* 2003. Efalizumab Study Group. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N. Engl. J. Med. **349:** 2004–2013.
27. BRINKMANN, V. 2004. FTY720: Mechanism of action and potential benefit in organ transplantation. Yonsei Med. J. **45:** 991–997.
28. ROVIEZZO, F. *et al.* 2004. Human eosinophil chemotaxis and selective in vivo recruitment by sphingosine 1-phosphate. Proc. Natl. Acad. Sci. USA **101:** 11170–11175.
29. YOPP, A.C. *et al.* 2004. FTY720-enhanced T cell homing is dependent on CCR2, CCR5, CCR7, and CXCR4: evidence for distinct chemokine compartments. J. Immunol. **173:** 855–865.
30. BENOIT, S., A. TOKSOY, E.B. BROCKER, *et al.* 2004. Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. Br. J. Dermatol. **150:** 1009–1012
31. SCHWARZ, M.K. & T.N.C. WELLS. 2002. New therapies that modulate chemokine networks. Nat. Rev. Drug Discov. **1:** 347–358.
32. KUNKEL, S.L. & N. GODESSART. 2002. Chemokines in autoimmunity: from pathology to therapeutics. Autoimmunity Rev. **1:** 313–320.
33. SZEKANECZ, Z. *et al.* 2003. Chemokines and chemokine receptors in rheumatoid arthritis. Semen. Immunol. **15:** 15–21.
34. HORUK, R. 2003. Development and evaluation of pharmacological agents targeting chemokine receptors. Methods **29:** 369–375.
35. MATTHYS, P. *et al.* 2001. AMD3100, a potent and specific antagonist of the stromal cell-derived factor chemokine receptor CXCR4, inhibits autoimmune joint inflammation in IFN-gamma receptor-deficient mice. J. Immunol. **167:** 4686–4692.
36. NAYA, A. *et al.* 2001. Design, synthesis, and discovery of a novel CCR1 antagonist. J. Med. Chem. **44:** 1429–1435
37. GARCIA-RAMALLO, E. *et al.* 2002. Resident cell chemokine expression serves as the major mechanism for leukocyte recruitment during local inflammation. J. Immunol. **169:** 6467–6473.
38. YANG, Y.F. *et al.* 2002. A non-peptide CCR5 antagonist inhibits collagen-induced arthritis by modulating T cell migration without affecting anti-collagen T cell responses. Eur. J. Immunol. **32:** 2124–2132.
39. GONG, J.H. *et al.* 2004. Post-onset inhibition of murine arthritis using combined chemokine antagonist therapy. Rheumatology (Oxford) **43:** 39–42.
40. PLATER-ZYBERK, C. *et al.* 1997. Effect of a CC chemokine receptor antagonist on collagen induced arthritis in DBA/1 mice. Immunol. Lett. **57:** 117–220.
41. QUINONES, M.P. *et al.* 2004. Experimental arthritis in CC chemokine receptor 2-null mice closely mimics severe human rheumatoid arthritis. J. Clin. Invest. **113:** 856–866.
42. IZIKSON, L. *et al.* 2000. Resistance to experimental autoimmune encephalomyelitis in mice lacking the CC chemokine receptor (CCR)2. J. Exp. Med. **192:** 1075–1080.
43. GAUPP, S. *et al.* 2003. Experimental autoimmune encephalomyelitis (EAE) in CCR2–/– mice. Am. J. Pathol. **162:** 139–150.
44. BHALAY, G. & A. DUNSTAN. 2004. Chemokine receptors and drug discovery-SMR meeting. I. Drugs **7:** 441–443.
45. GLADUE, R.P., S.H. ZWILLICH, A.T. CLUCAS & M.F. BROWN. 2004. CCR1 antagonists for the treatment of autoimmune diseases. Curr. Opin. Investig. Drugs **5:** 499–504.
46. PROUS SCIENCE PUBLISHERS. 2005. Prous Science Integrity database. Barcelona.

47. ELICES, M.J. 2002. BX-471 Berlex. Curr. Opin. Investig. Drugs **3:** 865–869 .
48. HARINGMAN, J.J. *et al.* 2003. Chemokine blockade and chronic inflammatory disease: proof of concept in patients with rheumatoid arthritis. Ann. Rheum. Dis. **62:** 715–721.
49. BERRY, K. *et al.* 2004. Evaluation of T0906487, a CXCR3 antagonist, in a phase 2a psoriasis trial [Abstract]. Inflammation Res. Suppl. **53:** pS222.

Chemokine Receptors

Attractive Targets for Drug Discovery

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ABSTRACT: Studies of two antibodies, efalizumab and natalizumab, have recently demonstrated that the blockade of leukocyte migration is of therapeutic benefit for the treatment of diseases such as psoriasis and multiple sclerosis. The role of chemokines in the control of cell traffic led to their receptors being considered one of the most promising family of targets aimed at disrupting cell recruitment in chronic inflammatory processes. Choosing the appropriate chemokine receptor for each disease was not easy, and the interpretation of target validation studies proved to be extremely difficult. Despite an intense effort in the search for chemokine receptor antagonists in the last decade, no compounds in advanced clinical trials exist as such. The inherent complexity of the family, the differences between the chemokine system in mice and men, and the species selectivity of small-molecule compounds could account for this fact. Pharmaceutical companies still believe in chemokine receptors as therapeutic targets, as demonstrated by the number of compounds reported to be in development. In the next years, the developmental progression of these compounds will reveal which target within the chemokine family is of real therapeutic value.

KEYWORDS: chemokines; leukocyte recruitment; G protein–coupled receptors; chronic inflammation; autoimmune diseases; drug discovery; target validation

INTRODUCTION TO CHEMOKINES: STRUCTURAL AND FUNCTIONAL CLASSIFICATION

Chemokines are a large family of small secreted proteins of 8–14 kDa that control cell trafficking. They are structurally divided into four classes—C, CC, CXC, and CX_3C—depending on the number and the relative position of their amino terminal cysteine residues (FIG. 1).[1] Individual chemokines are named using the acronyms of the structural class they belong to, followed by an L (for ligand) and their gene number.[2]

In the last decade, it has been clearly established that these mediators play a significant role in processes such as embryonic development, host defense, immune surveillance, inflammation, angiogenesis, autoimmunity, and cancer.[2–4] The biologic effects of chemokines are mediated by receptors expressed on the cell surface. Chemokine receptors are themselves classified according to the chemokine family

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they bind (FIG. 1). The nomenclature of the receptors is analogous to that of chemokines, using the family acronym followed by an R (for receptor) and a number that corresponds to the order of its discovery.[5] Chemokine receptors belong to class A of the G protein–coupled receptor (GPCR) superfamily. They are rhodopsin-like receptors that span the membrane seven times and are coupled to heterotrimeric $G\alpha\beta\gamma$ proteins.[6] Upon ligand–receptor interaction, different intracellular signaling pathways are activated, ultimately leading to cell mobilization and activation.[7]

From a functional point of view, chemokines can be divided into inflammatory, homeostatic, and dual function.[8] Inflammatory chemokines are induced by pathogens, cytokines, or growth factors and recruit effector leukocytes to sites of infection, inflammation, tissue injury, and tumor. CCR1, CCR2, CCR3, CCR5, CXCR2, XCR1, and CX_3CR1 are some examples of receptors that bind inflammatory chemokines. Homeostatic chemokines are expressed in bone marrow and lymphoid tissues and are involved in hematopoiesis, immune surveillance, and adaptive immune responses. The receptors for homeostatic chemokines (CCR7, CXCR4, and CXCR5) are expressed on B cells, follicular-helper T cells, central-memory T cells, and mature dendritic cells, among others. Chemokines that share properties of these two groups are classified as dual function. These chemokines are involved in adaptive immunity, T lymphopoiesis, dendritic cell development, and homing to particular anatomic compartments. Regulatory T cells, CLA4$^+$ cells (homing to skin), and

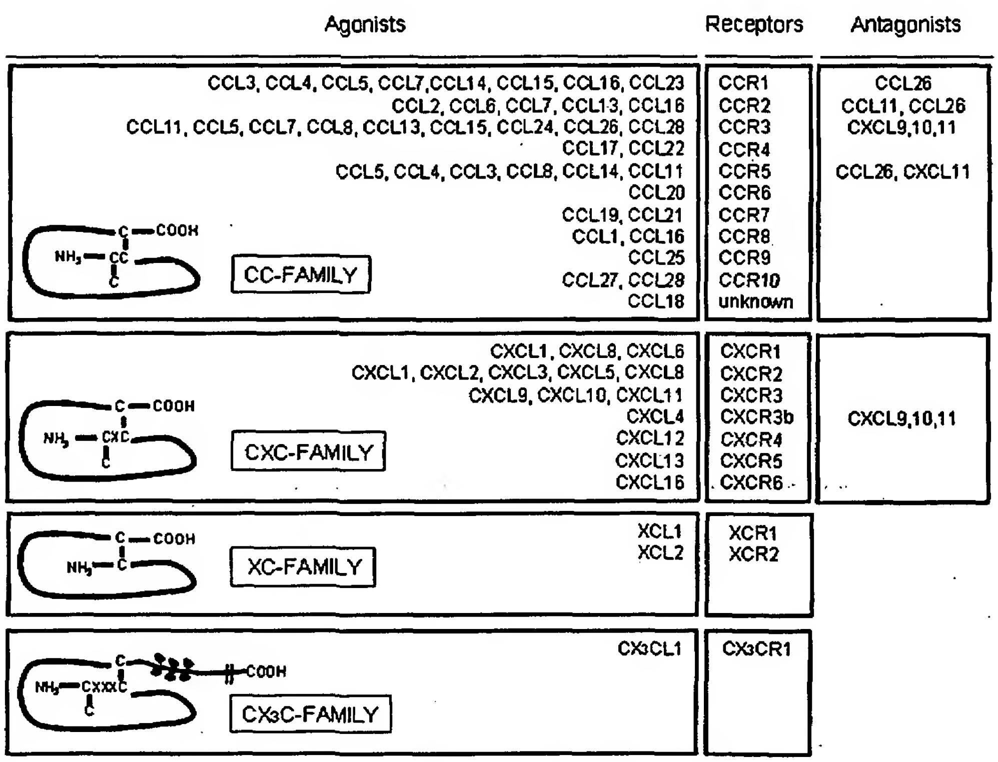

FIGURE 1. Structural classification of the chemokine superfamily. For each receptor, chemokines acting as agonists and antagonists are depicted. The systematic nomenclature of chemokines was used.[2]

$\alpha4\beta7^+$ cells (homing to intestinal mucosa) express receptors for these chemokines (CCR4, CCR6, CCR8, CCR9, CXCR3, and/or CXCR6). See Ref. 8 for a detailed description of the functional classification of chemokines.

A feature of the chemokine system is the complexity of the ligand–receptor interactions, especially evident in the inflammatory and dual-function chemokine groups. Thus, a particular chemokine (i.e., CCL5) may bind several receptors (CCR1, CCR3, and CCR5), and different chemokines (i.e., CXCL9, CXCL10, and CXCL11) may bind a single receptor (CXCR3). Some evidence suggest that in some cases ligand redundancy does not mean duplicity of functions. *In vitro* studies comparing the behavior of the two CCR7 ligands, CCL19 and CCL21, revealed differences in their affinity, their ability to desensitize the receptor,[9] and the signaling pathways evoked.[10] These results indicate that the roles of the two ligands were not merely redundant. Similar findings have been recently reported for the two ligands of human CCR4[11] and those of mouse CXCR2.[12] These results suggest that different ligands for the same receptor act in different compartments; one ligand would act at the endothelial surface to promote vascular recognition, and the other chemokine would engage the receptor within the tissue microenvironment to guide cellular localization. As expected, the ligand acting in the vascular compartment always exhibits a low capacity to desensitize the receptor, to allow cells to respond to the second stimulus.[9,11,12]

A series of discoveries made in the past 5 years have added a new degree of complexity. As FIGURE 1 shows, a chemokine may act either as an agonist or an antagonist, depending on the receptor it binds.[13–19] The antagonistic effect of some chemokines were revealed in *in vitro* studies, but it has also been reported to occur *in vivo*.[20,21] It has been postulated that the meaning of this effect is to increase the selectivity of cell recruitment.[20] A chemokine such as CXCL11, agonist of a receptor mainly expressed on T helper type 1 (Th1) cells (CXCR3), is at the same time an antagonist of the responses mediated by CCR3, a receptor expressed on Th2 cells. The opposite is also true: a chemokine such as CCL26 attracts Th2 cells *via* CCR3 cells while blocking CCR1- and CCR5-mediated responses on Th1 cells. In this scenario, the consequences of blocking a particular chemokine or a receptor *in vivo* could be unpredictable.

CHEMOKINES AND CELL MIGRATION

Leukocyte migration is a multistep process that takes place in homeostasis as well as in pathological conditions. In the last decade, the role of chemokines in the regulation of cell traffic has been clearly established. Proinflammatory stimuli induce the synthesis of chemokines by stromal cells, endothelial cells, and leukocytes. Chemokines may bind to heparin sulfate proteoglycans on the luminal surface of vascular endothelial cells, are exposed to the lumen of blood vessels (or high endothelial venules), and capture rolling leukocytes expressing the appropriate receptor. Chemokine binding activates the heterotrimeric G proteins coupled to the receptor. The α and the $\beta\gamma$ subunits dissociate and may activate several signaling pathways involving small GTPases (RAP1, RhoA, Rac) and/or kinases (PI_3K, atypical PKC, Pyk2), depending on the chemokine and the cell type.[22,23] This process results in a

change in the conformation and avidity of the leukocyte integrins, together with the formation of a polarity complex and the focal recruitment of integrins, culminating in transendothelial migration. Leukocytes are then guided to the target tissue, probably following the concentration gradient of chemokines bound to proteoglycans (haptotaxis). Once there, the high local concentration of chemokines would induce the phosphorylation and internalization of the receptor, making cells unresponsive to the same or other ligands of that receptor. Different chemokines may participate in different parts of the process, in a sequential manner, as it has been hypothesized to occur in the transmigration of lymphocytes from high endothelial venules.[22]

BLOCKADE OF LEUKOCYTE MIGRATION AS A THERAPEUTIC STRATEGY

The excessive infiltration of leukocytes is a hallmark of many autoimmune and chronic inflammatory diseases. Several approaches can be exploited to prevent cell recruitment to inflamed tissues, such as blocking adhesion molecules (selectins, integrins), or preventing the effect of chemotactic mediators such as peptidic (chemokines) or lipidic (eicosanoids, sphingolipids) mediators. TABLE 1 lists some agents, in different stages of development or in the market, that target cell migration.

TABLE 1. Therapies directed at blocking cell migration

Target family	Strategy	Drug name and company	Disease	Status
Integrins	Anti-α4 antibody	Tysabri® (natalizumab) Biogen and Elan	Multiple sclerosis	Launched
	Anti-CD11a antibody	Raptiva® (efalizumab) Xoma, Genetech, Serono	Psoriasis	Launched
Selectins	Selectin antagonist	Bimosiamose Revotar Pharm	Asthma, psoriasis	Phase II
	Anti-L-selectin antibody	Aselizumab Scil Biomedicals	Atherosclerosis, vascular injury	Phase II
Sphingosine	S1P receptor agonist	FTY-720 Novartis	Transplant rejection	Phase II
PGD_2	DP antagonist	L-888839 Merck Frosst	Seasonal allergic rhinitis	Phase I
	CRTh2 antagonist	Astra-Zeneca Pfizer	Allergic asthma, allergic rhinitis	Preclinical

Two biologicals that block lymphocyte integrins have validated cell traffic blockade as a therapeutic strategy. In November 2004, Tysabri® (natalizumab; Biogen Idec and Elan Corporation) was approved for the treatment of relapsing forms of multiple sclerosis.[24] This monoclonal antibody blocks the α4 integrin subunit, preventing T cells from transendothelial migration and probably from crossing the blood–brain barrier. Natalizumab has also demonstrated activity in a phase III clinical trial for Crohn disease.[25] Another monoclonal antibody, Raptiva® (efalizumab; Genentech and Xoma), was approved one year before for the treatment of chronic plaque psoriasis.[26] Raptiva is a humanized monoclonal antibody that binds human CD11a (a subunit of the LFA-1 integrin) and prevents the recruitment of T cells to the skin as well as their activation.

Treatment with both natalizumab and efalizumab is associated with an increase in the number of blood lymphocytes owing to the inhibition of their migration out of the vascular space. A different strategy is represented by FTY-720, a compound derived from the fungus *Isaria sinclairii*.[27] The compound is phosphorylated *in vivo* by the enzyme sphingosine kinase, forming FTY-720-P, a high-affinity nonselective agonist of sphingosine 1-phosphate receptor 1 ($S1P_1$), necessary for lymphocytes to exit lymphoid tissues. The compound induces the internalization of the receptor, preventing lymphocytes from responding to egress signals from circulating sphingosine 1-P (S1P), the natural ligand of $S1P_1$. The drug induces accumulation of naive and activated CD4 and CD8 T cells and B cells in lymph nodes and Peyer patches, preventing lymphocytes from being recruited at the graft. FTY720 (Novartis) is currently in phase III clinical trials for renal transplantation[27] and is also in development for multiple sclerosis. It is interesting that S1P has been described as inducing chemokine and/or chemokine receptor expression in several cell subsets, such as eosinophils and T cells.[28,29] Thus targeting S1P receptors represents an alternative strategy for modulating chemokine receptor expression.

Other agents in development include Bimosiamose®, a pan-selectin blocker in clinical trials of psoriasis and asthma, and low molecular weight antagonists of the prostaglandin D_2 (PGD_2) receptors, DP and CRTh2, in clinical trials of allergy and/ or asthma (TABLE 1).

CHEMOKINE RECEPTORS AS THERAPEUTIC TARGETS

Proinflammatory cytokines induce the synthesis of chemokines,[1,8] and blocking the biological effects of cytokines could be a nonselective way of inhibiting cell recruitment. This has been demonstrated to be the case for the anti-TNFα antibody Remicade® in psoriasis.[30] The only therapies, either in the market or in advanced clinical trials, that inhibit cytokine effects are biologicals—for example, anti-TNFα antibodies such as Remicade® and Humira®, soluble TNFα receptors such as Enbrel®, the IL-1 receptor antagonist Kineret®, the anti-IL-6 receptor MRA®, and the anti-IL-15 antibody HuMax-IL-15®. Probably the nature of cytokine receptors and the complex interactions established between cytokines and their receptors make this interaction difficult to be inhibited by small organic compounds.

The interest in chemokines as therapeutic targets increased with the discovery that their receptors, unlikely those of cytokines, are GPCRs. About half of the drugs currently in the market are either agonists or antagonists of GPCR, demonstrating

that at least some members of the family are "druggable" targets.[6] In 1996, just 5 years after the discovery of the first chemokine receptor, it was confirmed that chemokine receptor antagonists could be obtained.[31] The discovery of the role of CCR5 and CXCR4 as co-receptors in HIV infection gave researchers an impetus to search for antagonists of those receptors.

According to the information in the public domain, after a decade of drug discovery on chemokines, there are no compounds in advanced phases of development. The analysis of the difficulties found in drug discovery on chemokines have been reviewed[6,12] and is out of the scope of this chapter. Instead, we focus on the difficulty in interpreting results from target validation studies within the chemokine family.

TARGET VALIDATION ON CHEMOKINES: FROM MICE TO MEN

Evidence for the role of chemokines in disease states comes essentially from studies of animal models of disease and the analysis of human pathological samples.[7,32] These studies provided a list of potential targets for the treatment of diseases such as multiple sclerosis, atherosclerosis, psoriasis, asthma, arthritis, diabetes, and cancer.[3,6,7,32] Most of these targets correspond to receptors for inflammatory chemokines, characterized by redundancy and promiscuity. Would inhibition of a single receptor be enough to achieve efficacy? Which was the best target for each pathology? Choosing the target was difficult, especially for diseases like rheumatoid arthritis (RA), in which more than six potential targets have been suggested.[33]

Validation of the candidate compound in animal models was desirable for reducing failures in the clinic. However, target validation with small molecule receptor antagonists soon proved to be difficult. As occurs for antagonists of other GPCRs with peptidic ligands,[6] compounds often exhibit species selectivity, thus cannot be used in mouse or rat models. This explains why only limited information about the *in vivo* effects of receptor antagonists exists.[34–38]

Biological reagents (antibodies or modified natural ligands) and knockout mice are also good validation tools. However, results obtained using different validation strategies sometimes led to contradictory conclusions. The receptors CCR2 and CCR5, previously validated for arthritis by two independent groups using modified chemokines,[39,40] have since been devalidated using knockout mice.[41] These studies showed that the lack of CCR5 had no impact on the progression of arthritis, whereas CCR2 knockout mice developed more severe disease than did controls.[41]

Independent groups working with the same chemokine receptor knockout mice have also obtained contradictory results. This is the case for CCR2 and multiple sclerosis.[42,43] Factors such as the use of different experimental protocols and/or the mouse strain have been argued to explain these differences.

The true target validation occurs in the clinic, but these data are still missing. Several compounds have progressed to clinical trials and failed,[31] and the reasons are not always known. Toxicity issues, a deficient ADME profile, and an inadequate target can account for this fact. However, there is still an intense activity in the field, as illustrated by the number of agents targeting chemokine receptors currently in development (TABLE 2). As an update of previous reviews,[12,31,44,45] a more detailed explanation of the situation of the antagonists of CCR1, CCR2, and CXCR3 receptors is given below.

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EXAMINER	
O'DELL, DAVID K	
ART UNIT	**PAPER NUMBER**
1625	
MAIL DATE	**DELIVERY MODE**
12/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/575,522	HOSSAIN, NAFIZAL
	Examiner	Art Unit
	David K. O'Dell	1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 16 November 2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-10 and 12-18 is/are pending in the application.

4a) Of the above claim(s) 8,10 and 12-18 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7, 9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10, 12-18 are pending in the current application.

2. This is a National Stage of PCT/SE2004/001476, filed October 14, 2004, which claims priority to Swedish Application Serial No. 0302755-4, filed October 17, 2003.

Response to Remarks Arguments

3. Applicant's arguments filed November 13, 2007 have been fully considered but they are not persuasive. The rejections under 35 U.S.C. 103 (a) are withdrawn in light of applicant's statement of common assignment. The rejection for solvate is withdrawn, it is noted that claim 7 also appears to contain solvate, which was unintentionally overlooked by the examiner. Rather than repeat another rejection and based upon applicant's willingness to delete this term, the examiner is not rejecting this claim for "solvate" and depends upon the applicant to remove this term. The rejections for scope of enablement are maintained as the directions for the preparation and use of the compounds commensurate in scope with the claims has not been provided. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again vide infra). It would appear that the applicant is arguing that essentially any molecule, even molecules of unknown structure, can be made without undue experimentation. This is in fact not the situation in the chemical arts. As stated in a recent book on the subject:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and

synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work......Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].......even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]................. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]........ As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].........Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even

> simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]….." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

The examiner (*vide infra* and in the previous action) serve to show the scope that is enabled by the specification, in terms of the compounds, and the teaching of the prior art. A recent ruling by the Federal circuit discusses enablement in the context of the automotive art, but there is little difference in the position of the court and the position of the examiner instant case, ATI v. BMW et. al. (Fed. Cir. 2007):

> "We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007). In that case, the invention was a front-loading fluid injector system with a replaceable syringe capable of at 1373. We construed the asserted claims, as urged by the patentee, to include an injector with and without a pressure jacket. Although the specification clearly enabled an injector with a pressure jacket, we concluded that it did not enable an injector without such a jacket and that the claims were invalid for lack of enablement. at 1379. We stated that there "must be 'reasonable enablement of the scope of the range' which, in this case, includes both injector systems with and without a pressure jacket." withstanding high pressure for delivering a contrast agent to a patient. Id. Id. Id. at 1380 (internal citation omitted).
>
> Similarly, in this case, the claim construction of the relevant claim limitation resulted in the scope of the claims including both mechanical and electronic side impact sensors. Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors. Electronic side impact sensors are not just another known species of a genus consisting of sensors, but are a distinctly different sensor compared with the well-enabled mechanical side impact sensor that is fully discussed in the specification. Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both electronic and mechanical side impact sensors, which the specification fails to do. We stated in Liebel: "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Id. at 1380. ATI sought to have the scope of the claims of the '253 patent include both mechanical and electronic side impact sensors. It succeeded, but then was unable to demonstrate that the claim was fully enabled. Claims must be enabled to correspond to their scope."

The very limited disclosure and the inordinate amount of experimentation required to practice the invention, clearly warrant the conclusion made by the examiner, which was supported by references testifying to the state of the art and its unpredictability. This action is made **FINAL**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

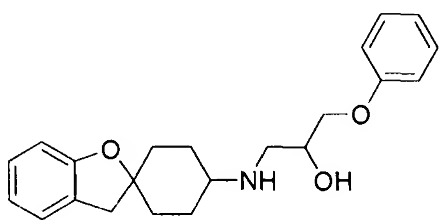
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10 of copending Application No. 10/579,545 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

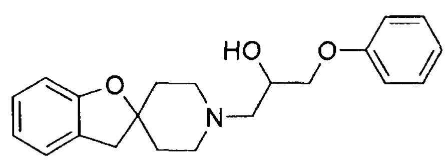
Determination of the scope and content of the prior art

(MPEP 2141.01)

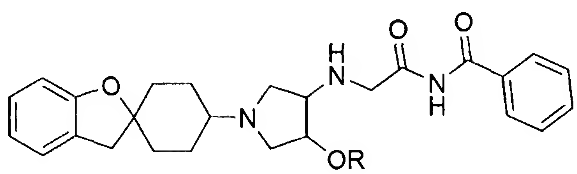
Xue et. al. teaches spiro[benzofuran-2,1'-cyclohexan]-4'-amines that are chemokine antagonists. 10/579,545 teach spiro[benzofuran-2,4'-piperidines bearing a 1-phenoxy-3-propan-2-ol substituent on the piperidinyl nitrogen atom. This relationship is illustrated graphically in Figure 1.



Instant case



U.S. Application 10/520,699

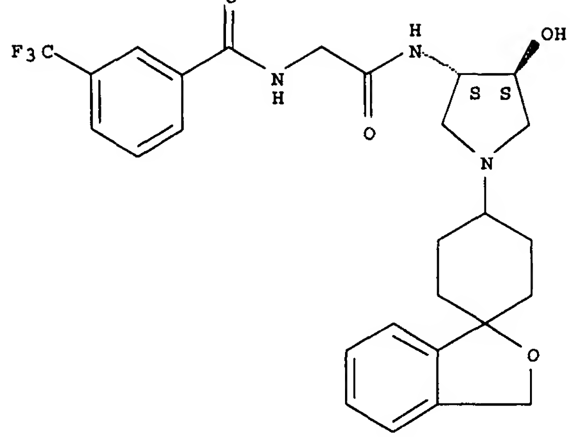


Xue et. al.

Figure 1. Structures of compounds that form the basis of the obviousness rejection as compared to the instant invention.

Some of the compounds disclosed by Xue are show below:

Registry #: 709018-09-7



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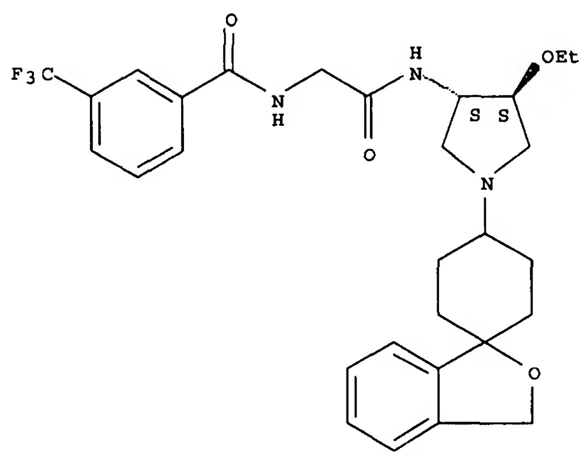


Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene group. By inserting a what is formally a methylene (CH_2 actually CH in the ring and H on N) into the compounds of Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite a spiro[benzofuran-2,1'-cyclohexan]-4'-amine is produced, which is a core

pharmacophore of chemokine antagonism. These relationships are illustrated graphically in Figure 2.

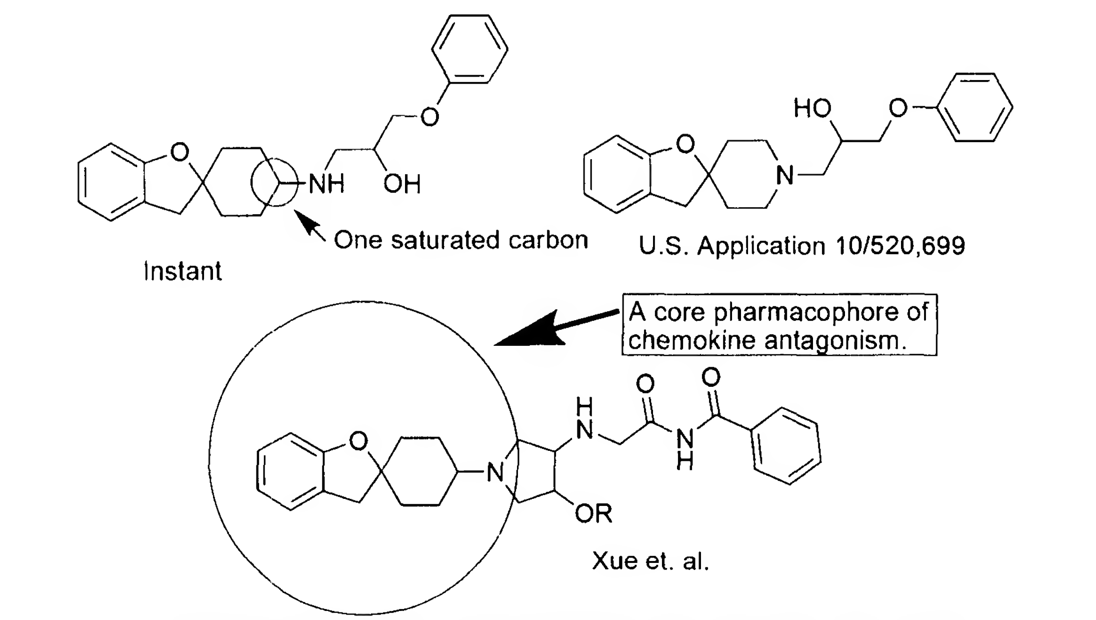


Figure 2. The differences between the compounds of the instant case and those of the prior art.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner

concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12 of copending Application No. 10/581,171 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. This is a provisional obviousness-type double patenting rejection.

7. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, 14 of copending Application No. 10/583,468 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. Although claim 9 is apparently a claim for "a claim".

8. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13 of copending Application No.

10/520,699 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here.

This is a provisional obviousness-type double patenting rejection.

9. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claim 1-7, 9, 11 of commonly assigned copending Application No. 11/744,659. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

10. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-7, 9, 11 of commonly assigned copending Application No. 11/744,677. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common

subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6, 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill:** One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually

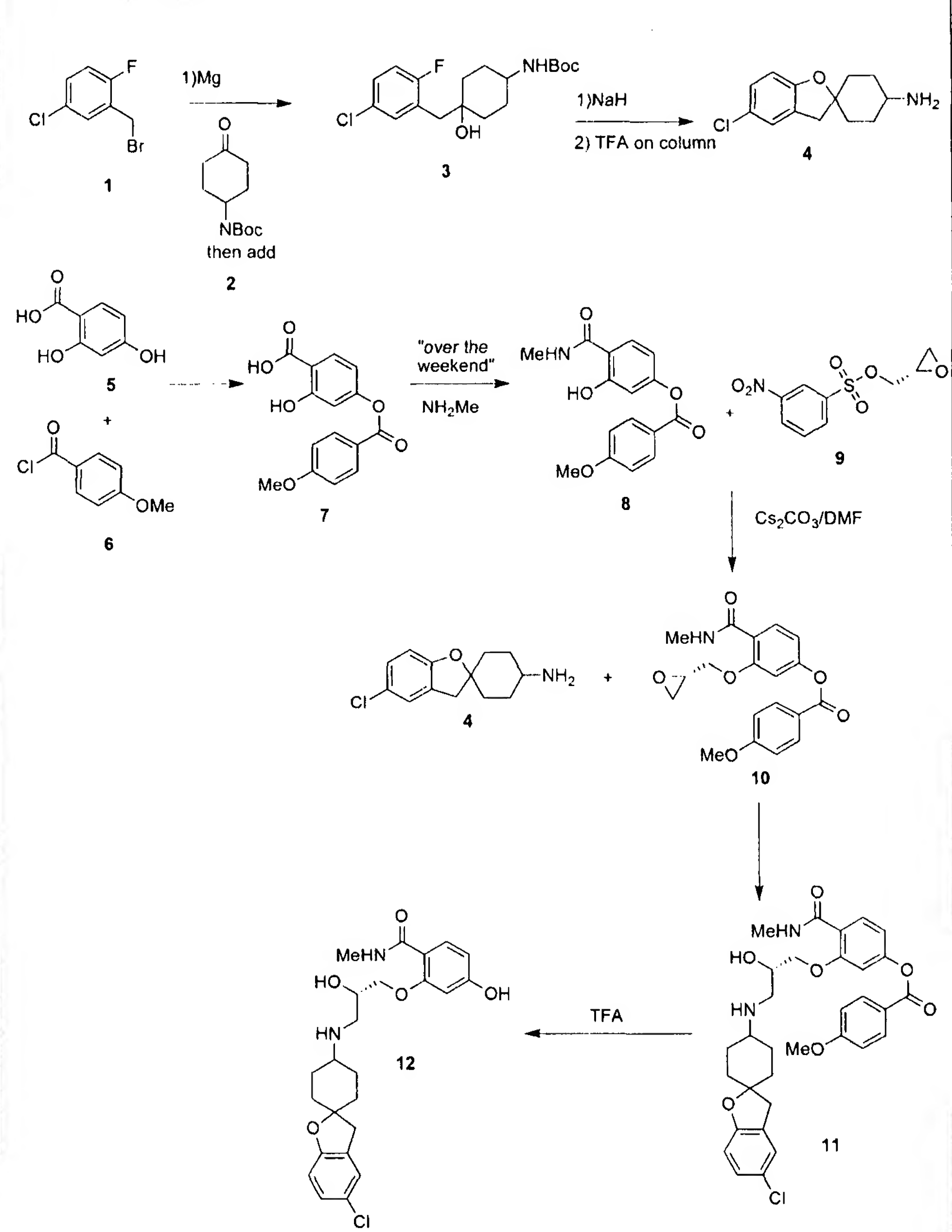
> implies will be able to appraise such work......Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious).................." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The synthetic route and starting materials that the applicant has provided to make the scope of this invention has been reproduced below as Scheme1:



Scheme 1. The chemistry relied on to construct applicant's compounds.

The key materials here are the □-bromo-2-fluoro-toluene derivative **1**, the N-Boc-4-amino cylcohexanone **2**, phenols such as **8** bearing amide groups, and glycidols **9**. A search for each of these materials in the Aldrich Chemical Company catalog (St. Louis, MO) was conducted, the reulsts of which are reproduced below:

SIGMA-ALDRICH | Home

Search |

Enter Search Criteria

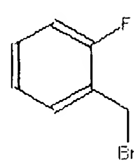
Search CLEAR

Search Type: SubStructure (2D)

Structure:

CLR NEW DEL D-R +/- UDO JME

C N O S F Cl I X



JME Editor courtesy of Peter Ertl. Novartis

SMILES: Load

MW: Between &

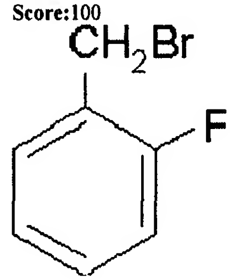
Results / Page: 50

Total Hits: 2000

More Options

Search Results 1-15 of 15 in 0.0 sec New Search Export

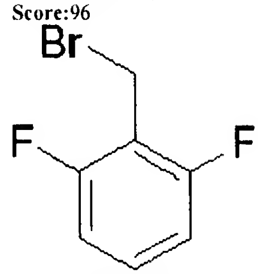
Sort By:
MW

	Compound Properties	Structure Score:100	Add	Prod. #	Purity
Name:	**2-Fluorobenzyl bromide**			209511	98%
IUPAC:	**1-(bromomethyl)-2-fluorobenzene**				
MF:	C_7H_6BrF				
CAS #:	446-48-0				
MW:	189.02				
MDL #:	MFCD00000324				
BP:	84 - 85 °C				
FP:	181				
d:	1.5670				

Zoom In

Name: **2,6-Difluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1,3-difluorobenzene**
MF: $C_7H_5BrF_2$
CAS #: 85118-00-9
MW: 207.02
MDL #: MFCD00000329
FP: 230

Score:96



83141 purum, ≥95.0% (GC)
264431 97%

Zoom In

Name: **2,5-Difluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1,4-difluorobenzene**
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CAS #: 85117-99-3
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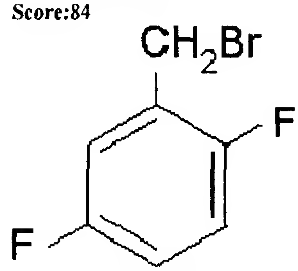
FP: 60
d: 1.6090

Score:84



264423 98%

Zoom In

Name: **2,3-Difluorobenzyl bromide**
IUPAC: **1-(bromomethyl)-2,3-difluorobenzene**
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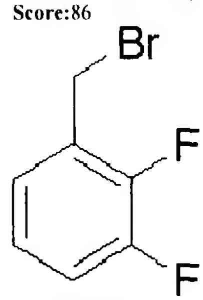
FP: 194
d: 1.6280

Score:86



68318 ≥99.5% (GC)
74259 purum, ≥99.5% (GC)
265314 98%

Zoom In

Name: **2,4-Difluorobenzyl bromide**
IUPAC: **1-(bromomethyl)-2,4-difluorobenzene**
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MW: 207.02
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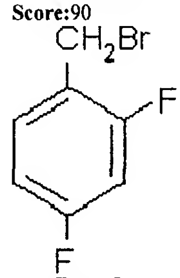
d: 1.6130

Score:90

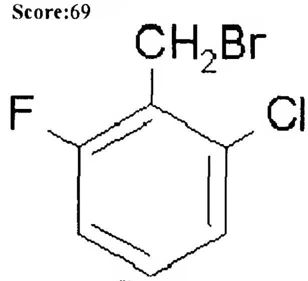


264415 98%

Zoom In

Name: **2-Chloro-6-fluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1-chloro-3-fluorobenzene**
MF: C_7H_5BrClF
CAS #: 68220-26-8
MW: 223.47
MDL #: MFCD00040126
FP: 230
d: 1.6290

Score:69



539090 96%

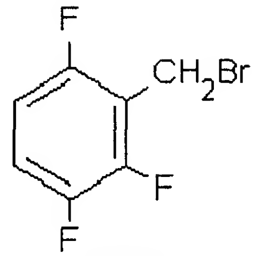
Zoom In

Name: **2,3,6-Trifluorobenzyl bromide**
IUPAC: **2-(bromomethyl)-1,3,4-trifluorobenzene**
MF: $C_7H_4BrF_3$
CAS #: 151412-02-1

Score:84

449407 97%

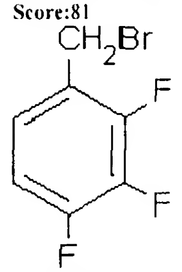
MW: 225.01
MDL #: MFCD00061208
BP: 114 °C
FP: 195
d: 1.7180



Zoom In

Name: 2,3,4-Trifluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3,4-trifluorobenzene
MF: $C_7H_4BrF_3$
CAS #: 157911-55-2
MW: 225.01
MDL #: MFCD00061233
FP: 195
d: 1.71

Score:81

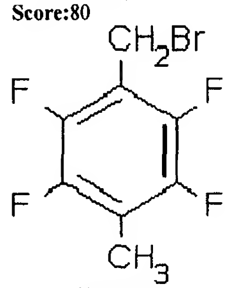


Zoom In

554685 97%

Name: 1-Bromomethyl-4-methyl-2,3,5,6-tetrafluorobenzene
IUPAC: 1-(bromomethyl)-2,3,5,6-tetrafluoro-4-methylbenzene
MF: $C_8H_5BrF_4$
CAS #: 92814-00-1
MW: 257.02
MDL #: MFCD03001155
FP: 199

Score:80

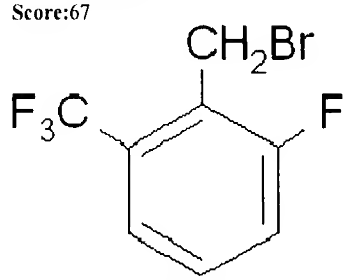


Zoom In

556491 97%

Name: 2-Fluoro-6-(trifluoromethyl)benzyl bromide
IUPAC: 2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene
MF: $C_8H_5BrF_4$
CAS #: 239087-08-2
MW: 257.02
MDL #: MFCD00082477
FP: 225

Score:67

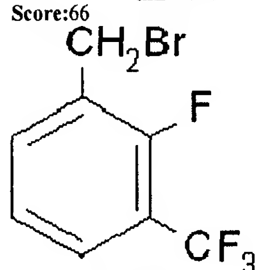


Zoom In

539627 98%

Name: 2-Fluoro-3-(trifluoromethyl)benzyl bromide
IUPAC: 1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene
MF: $C_8H_5BrF_4$
CAS #: 184970-25-0
MW: 257.02
MDL #: MFCD00061172

Score:66



Zoom In

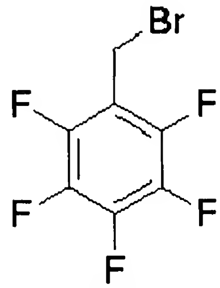
538094 97%

Name: 2,3,4,5,6-Pentafluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene
MF: $C_7H_2BrF_5$
CAS #: 1765-40-8
MW: 260.99
MDL #: MFCD00000299
BP: 174 - 175 °C

Score:81

17910 puriss., ≥99.0% (GC)
101052 99%
33001 ampule of 5 g

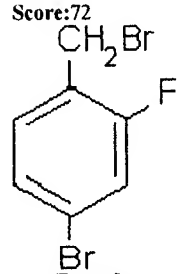
FP: 181
d: 1.7280



Zoom In

Name: 4-Bromo-2-fluorobenzyl bromide
IUPAC: 4-bromo-1-(bromomethyl)-2-fluorobenzene
MF: $C_7H_5Br_2F$
CAS #: 76283-09-5
MW: 267.92
MDL #: MFCD00055467

Score:72

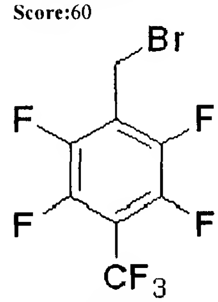


Zoom In

477559 98%

Name: 2,3,5,6-Tetrafluoro-4-(trifluoromethyl)benzyl bromide
IUPAC: 1-(bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene
MF: $C_8H_2BrF_7$
CAS #: 76437-40-6
MW: 310.99
MDL #: MFCD00191855
FP: 210
d: 1.8640

Score:60

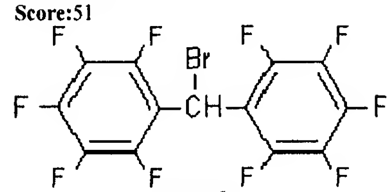


Zoom In

87285 purum, ≥97.0% (GC)
406406 98%

Name: DECAFLUOROBENZHYDRYL BROMIDE
IUPAC: DECAFLUOROBENZHYDRYL BROMIDE
MF: $C_{13}HBrF_{10}$
CAS #: 5736-4-9--2
MW: 427.04
MDL #: MFCD00017901

Score:51



Zoom In

Most disturbingly we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made. We can see that R_1 can be nothing but fluoro, trifluormethyl or chloro.

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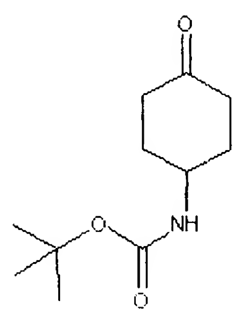
Search Type: SubStructure (2D)

Structure:

CLR NEW DEL D-R +/- UDO JME

C N O S F Cl Br I X



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Search Results 0-0 of 0 in 1.0 sec

Sort By:
MW

Compound Properties	Structure	Add

No such cyclohexanones appear to be commercially available. While many phenols such as **8** are commercial, it would appear that the amide functionality (reverse as well) is required for activity, based on the fact that applicant has no examples of compounds that are not amides (in the ortho position) and the fact that Xue et. al. (supra) require the amide moiety for antagonism. To the examiners knowledge only one nosylglycidol, namely compound **9,** is commercial. Substituents should be limited to lower alkyl.

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required staring materials of formula **1**, **2**, **8,** and **9** are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference

materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the

bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730,734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *Inre Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). This is because it is not obvious from the disclosure of one species, what other species will work.

If such starting materials could be obtained compounds could be obtained it is very clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by Grignards (Jie Jack Li *Name Reactions A Collection of Detailed Reaction Mechanisms* "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur (Knochel et. al. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302 –4320). The

"alkylhalo" compounds will undergo metal halogen exchange when in the presence of a Grignard (Knochel ibid.).

Another disturbing feature of what is before the examiner, is the fact that it appears that no assays were performed. These compounds may perform in this assay however this has not been asserted. There is no support in the specification for the use of these compounds as chemokine antagonists. While applicant states on pg. 40 "Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of M1P-1α chemokine." No evidence is given that these compounds actually were shown to have this activity. Given that similar compounds have the activity we can assume they have this activity (supra). The assumption that a chemokine receptor is involved may be incorrect, given that agonism at other GPCRs (δ-opiod receptors for instance), can lead to down regulation of chemokine receptors via heterodimers or higher oligomer complex formation (Chen et. al. *European Journal of Pharmacology* **2004**, *483*, 175-186.). The complete receptor profile of THP-1 cells is not known. Applicant may consider a binding assay as in Carroll et. al. WO 00/014086 cited by applicant ref. AG pg. 34:

plate counter.

The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ^{125}MIP-1α.

or Bondinell et. al. WO 01/64213 A1 pg. 23-25 cited by applicant ref. AH

<u>Biological Data:</u>

<u>CCR5 Receptor Binding Assay</u>

CHO cell membranes (0.25 x10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 or mCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 µM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists). Alternatively, this CCR5 receptor functional assay was performed on murine CCR5 (mCCR5) with a RANTES concentration of 2nM.

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 µM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators

Conclusion

12. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RDesai
RITA DESAI
PRIMARY EXAMINER
12/12/07

Notice of References Cited	Application/Control No. 10/575,522	Applicant(s)/Patent Under Reexamination HOSSAIN, NAFIZAL	
	Examiner David K. O'Dell	Art Unit 1625	Page 1 of 1

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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.
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F. Zaragoza Dörwald

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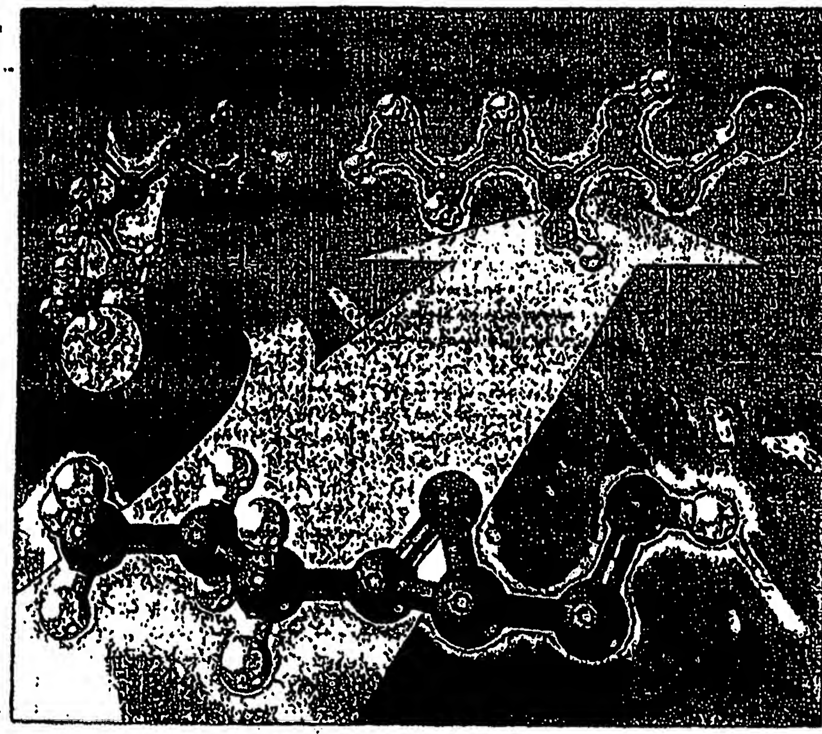
Side Reactions in Organic Synthesis

A Guide to Successful Synthesis Design



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Florencio Zaragoza Dörwald

Side Reactions in Organic Synthesis

A Guide to Successful Synthesis Design

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Preface

Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why.

Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.

This book attempts to highlight the competing processes and limitations of some of the most common and important reactions used in organic synthesis. Awareness of these limitations and problem areas is important for the design of syntheses, and might also aid elucidation of the structure of unexpected products. Two chapters of this book cover the structure–reactivity relationship of organic compounds, and should also aid the design of better syntheses.

Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious). Nevertheless, I have ventured to describe some reactions as difficult or impossible. A talented chemist might, however, succeed in performing such reactions anyway, for what I congratulate him in advance. The aim of this book is not to stop the reader from doing bold experiments, but to help him recognize his experiment as bold, to draw his attention to potential problems, and to inspire, challenge, and motivate.

Side Reactions in Organic Synthesis. Florencio Zaragoza Dörwald

ISBN: 3-527-31021-5

1
Organic Synthesis: General Remarks

1.1
Introduction

Organic reactions almost never yield exclusively the desired product. Students learn this when they perform their first synthesis in the laboratory, for example the synthesis of anisole from phenol. Although the starting materials, the intermediates, and the product are all colorless, the reaction mixture will turn uncannily dark. This darkening shows that in reality much more is going on in addition to the expected process, and that obviously quite complex chemistry must be occurring, giving rise to extended conjugated polyenes from simple starting materials. Fortunately these dyes are usually formed in minute amounts only and the student will hopefully also learn not to be scared by color effects, and that even from pitch-black reaction mixtures colorless crystals may be isolated in high yield.

Because most reactions yield by-products and because isolation and purification of the desired product are usually the most difficult parts of a preparation, the work-up of each reaction and the separation of the product from by-products and reagents must be carefully considered while planning a synthesis. If product isolation seems to be an issue, the work-up of closely related examples from the literature (ideally two or three from different authors) should be studied. Many small, hydrophilic organic compounds which should be easy to prepare are still unknown, not because nobody has attempted to make them, but because isolation and purification of such compounds can be very difficult. Therefore the solubility of the target compound in water and in organic solvents, and its boiling or melting point, should be looked up or estimated, because these will aid choice of the right work-up procedure.

The chemical stability of the target compound must also be taken into account while planning its isolation. Before starting a synthesis one should also have a clear idea about which analytical tools will be most appropriate for following the progress of the reaction and ascertaining the identity and purity of the final product. Last, but not least, the toxicity and mutagenicity of all reagents, catalysts, solvents, products, and potential by-products should be looked up or estimated, and appropriate precautionary measures should be taken.

Side Reactions in Organic Synthesis. Florencio Zaragoza Dörwald

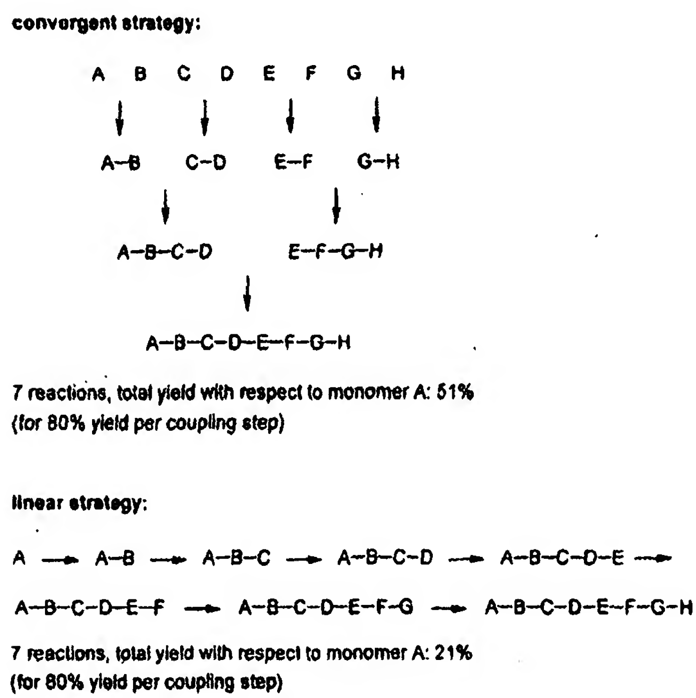
ISBN: 3-527-31021-5

1.2
Synthesis Design

The synthesis of a structurally complex compound requires careful retrosynthetic analysis to identify the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity. It is critical to keep the synthesis as short as possible, because, as discussed throughout this book, each reaction can cause unexpected problems, especially when working with structurally complex intermediates. Also for synthesis of "simple-looking" structures several different approaches should be considered, because even structurally simple compounds often turn out not to be so easy to make as initially thought.

1.2.1
Convergent vs Linear Syntheses

If a target compound can be assembled from a given number of smaller fragments, the highest overall yields will usually be obtained if a convergent rather than linear strategy is chosen (Scheme 1.1). In a convergent assembly strategy the total number of reactions and purifications for all atoms or fragments of the target are kept to a



Scheme 1.1. Convergent and linear assembly strategies.

minimum. If a linear strategy is chosen the first fragment (A in Scheme 1.1) will be subjected to a large number of reactions and purifications, and the total yield with regard to this first fragment will be rather low. Syntheses should be organized in such a way that expensive and/or structurally complex fragments are subjected to the fewest possible number of transformations.

1.2.2 Retrosynthetic Analysis

1.2.2.1 Introduction

When planning a synthesis, the most suitable starting materials should be chosen. These should be structurally and/or stereochemically as closely related to the target as possible, to keep the synthesis brief. The first steps of a good synthesis may even be low-yielding (if the products are easy to purify), because at these early stages little work and reagents have been invested and the intermediates are still cheap. Poor yields at later stages of a multistep synthesis, however, strongly reduce its usefulness, because most steps of the synthesis will have to be run on a large scale, using large amounts of solvents and reagents, to obtain a small amount only of the final product, which will, accordingly, be rather expensive.

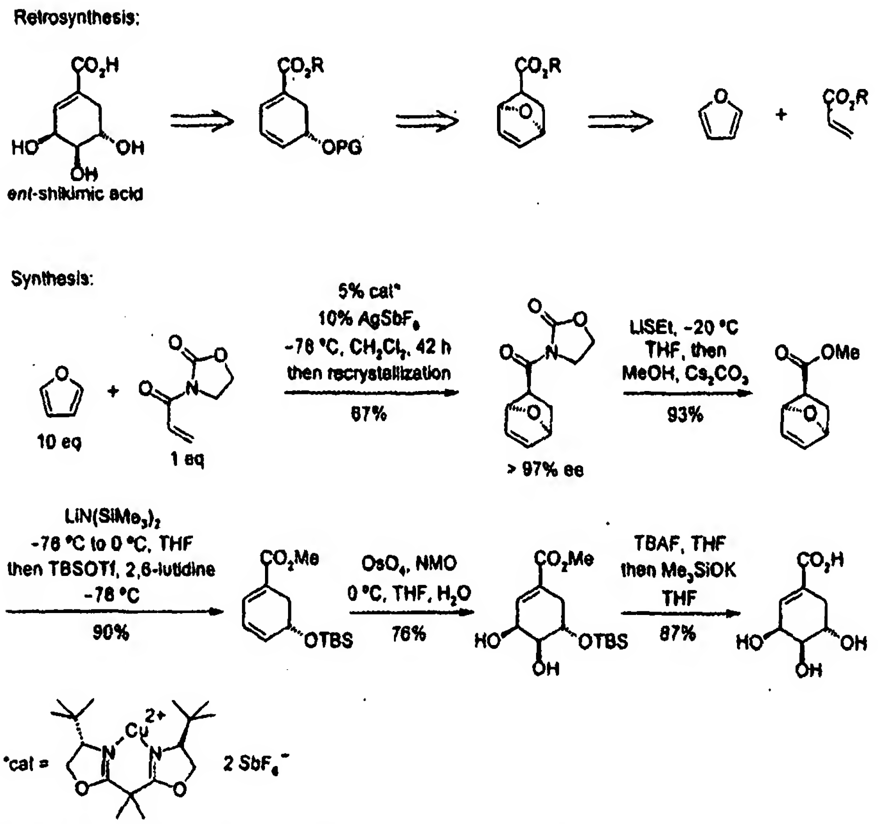
In a retrosynthesis the easiest bonds to make are often cleaved first (i.e. these bonds will be made at the end of the synthesis), yielding several fragments which can be joined together at late stages of the synthesis, using straightforward and high-yielding chemistry. Such reactions would usually be condensations, for example acetal, amide, or ester formation, or the formation of carbon–heteroatom bonds, but might also be high-yielding C–C bond-forming reactions if the required reaction conditions are compatible with all the structural elements of the final product.

If the target contains synthetically readily accessible substructures (e.g. cyclic elements accessible by well established cycloaddition or cyclization reactions), these might be chosen as starting point of a disconnection [1]. If such substructures are not present, their generation by introduction of removable functional groups (e.g. by converting single bonds into double bonds or by formal oxidation of methylene groups to carbonyl groups, Scheme 1.5) should be attempted. If this approach fails to reveal readily accessible substructures, the functional groups present in the target structure which might assist the stepwise construction of the carbon framework must be identified, and the bonds on the shortest bond paths between these groups should be considered as potential sites of disconnection (Scheme 1.3). Retro-aldol or Mannich reactions, optionally combined with the "Umpolung" of functional groups, have been the most common and successful tools for disconnection of intricate carbon frameworks, but any other, high-yielding C–C bond-forming reaction can also be considered. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures.

1.2.2.2 Shikimic Acid

In Scheme 1.2 one possible retrosynthetic analysis of the unnatural enantiomer of shikimic acid, a major biosynthetic precursor of aromatic α-amino acids, is sketched. Because *cis* dihydroxylations can be performed with high diastereoselectivity and yield, this step might be placed at the end of a synthesis, what leads to a cyclohexadienoic acid derivative as an intermediate. Chemoselective dihydroxylation of this compound should be possible, because the double bond to be oxidized is less strongly deactivated than the double bond directly bound to the (electron-withdrawing) carboxyl group.

Despite being forbidden by the Baldwin rules (5-*endo*-trig ring opening; see Section 9.2), cyclohexadienoic acid derivatives such as that required for this synthesis can be prepared by base-induced ring scission of 7-oxanorbornene derivatives, presumably because of the high strain-energy of norbornenes. The required 7-oxanorbornene, in turn, should be readily accessible from furan and an acrylate via the

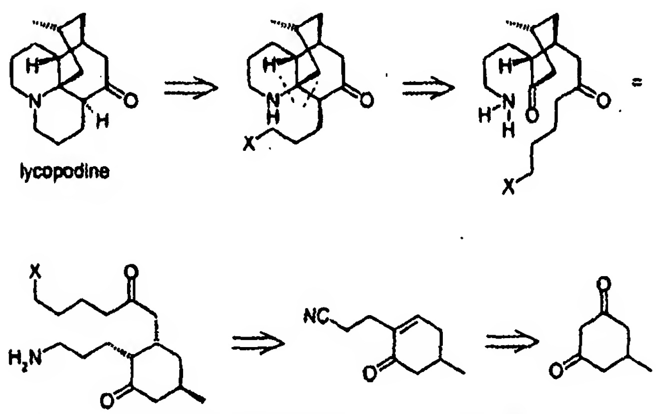


Scheme 1.2. Retrosynthetic analysis and synthesis of *ent*-shikimic acid [2].

Diels–Alder reaction. With the aid of an enantiomerically pure Lewis acid this Diels–Alder reaction yields a highly enantiomerically enriched 7-oxanorbornene, so that the remaining steps of this elegant synthesis only need to proceed diastereoselectively and without racemization.

1.2.2.3 Lycopodine

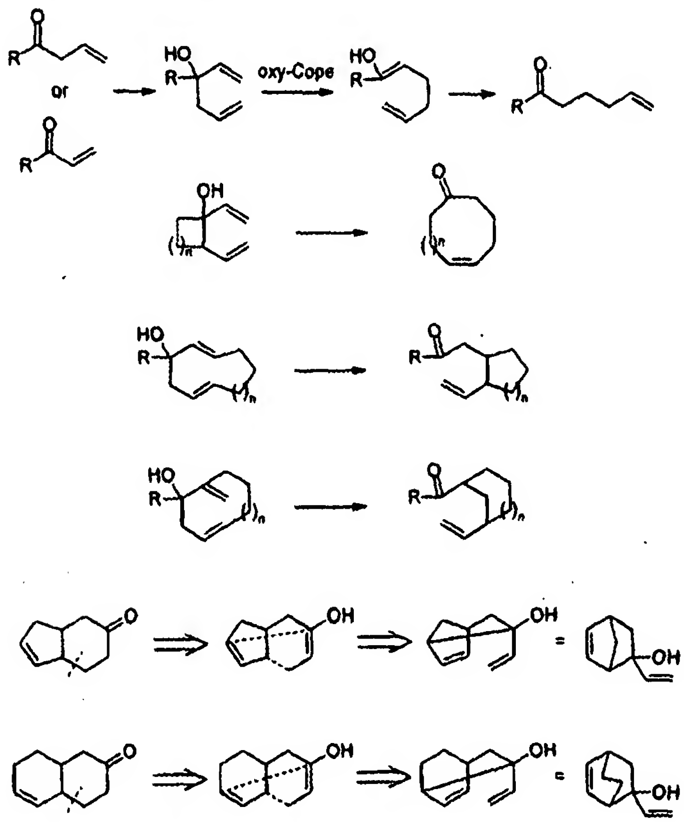
A further target which contains a readily accessible and easily recognizable substructure is the alkaloid lycopodine. Being a β-amino ketone, a possible retrosynthesis could be based on an intramolecular Mannich reaction, as outlined in Scheme 1.3. In this case two of the targets four rings would be generated in one step by a Mannich condensation; this significantly reduces the total number of steps required. A robust, intramolecular N-alkylation was chosen as last step. Realization of this synthetic plan led to a synthesis of racemic lycopodine in only eight steps with a total yield of 13 % [3]. Fortunately the Mannich reaction yielded an intermediate with the correct relative configuration.



Scheme 1.3. Retrosynthesis of lycopodine based on an intramolecular Mannich reaction [3].

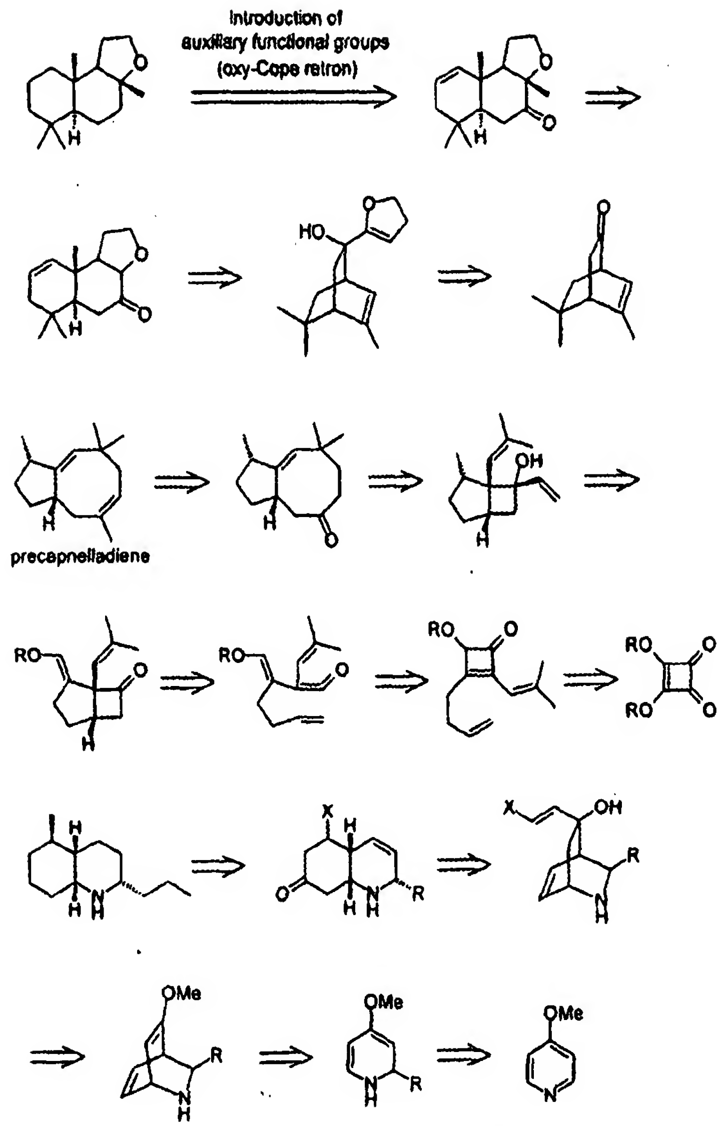
1.2.2.4 The Oxy-Cope Rearrangement

Less obvious than the retrosyntheses discussed above are those based on intramolecular rearrangements, because these often involve a major change of connectivity between atoms. For instance, exploitation of oxy-Cope rearrangements as synthetic tools requires some practice and the ability to recognize the substructures accessible via this reaction from readily available starting materials. Oxy-Cope rearrangements yield 4-penten-1-yl ketones by formal allylation of a vinyl ketone at the β position or γ-vinylation of an allyl ketone (Scheme 1.4). This rearrangement can be used to prepare decalins [4] or perhydroindenes [5, 6] from bicyclo[2.2.2]octenones or norbornenones, respectively, which can be prepared by using the Diels–Alder reaction. Moreover, oxy-Cope rearrangements may be used for ring expansions or contractions.



Scheme 1.4. The oxy-Cope rearrangement.

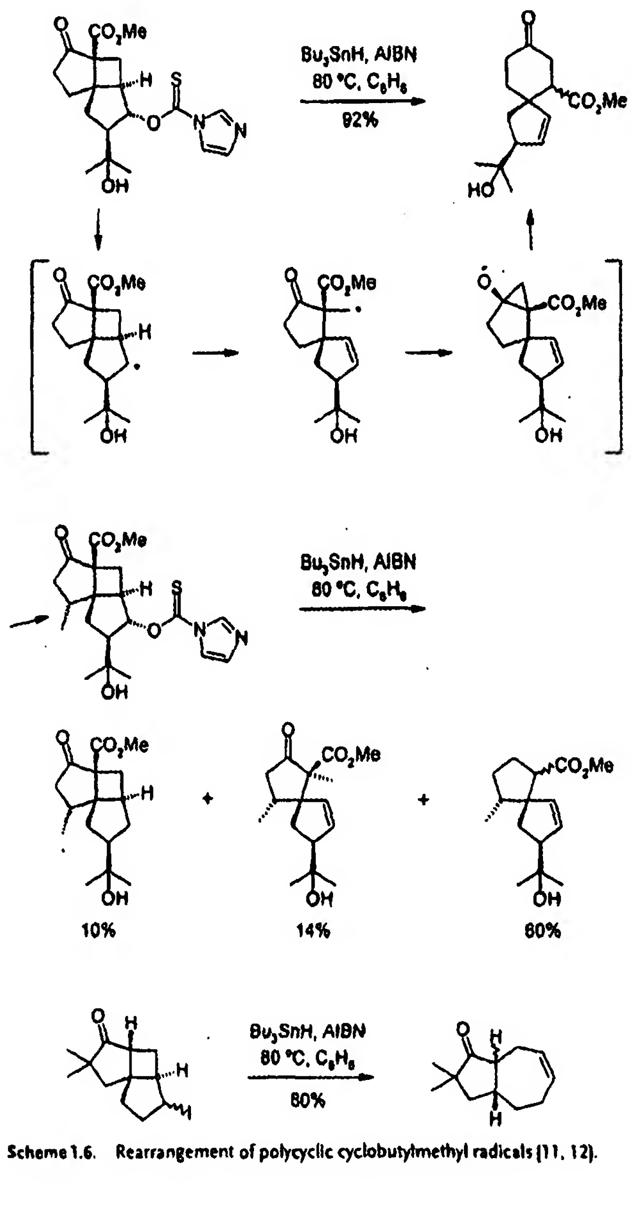
Numerous natural products have been prepared using the oxy-Cope rearrangement as the key step [5], in particular, and with high virtuosity, by the group of L.A. Paquette [4, 6, 7]. Three examples of retrosynthetic analyses of natural products or analogs thereof based on the oxy-Cope rearrangement are shown in Scheme 1.5. Because all the products are devoid of a keto group, the required 4-penten-1-yl ketone substructure (i.e. the oxy-Cope retron [1]) must be introduced during the retrosynthesis in such a way that accessible starting materials result.



Scheme 1.5. *Retrosynthesis of an ambergris-type ether, of precapnelladiene, and of an alkaloid based on the oxy-Cope rearrangement [8–10].*

1.2.2.5 Conclusion

As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. Therefore, while planning a multistep synthesis, it is important to keep the total number of steps as low as possible.



Scheme 1.6. Rearrangement of polycyclic cyclobutylmethyl radicals [11, 12].

Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed [11]. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity.

Examples of closely related starting materials which upon treatment with the same reagents yield completely different products are sketched in Scheme 1.6. The additional methyl group present in the second starting material slows addition to the carbonyl group of the radical formed by ring scission of the cyclobutane ring, and thus prevents ring expansion to the cyclohexanone. Removal of the methoxycarbonyl group leads to cleavage of a different bond of the cyclobutane ring and thereby again to a different type of product [12].

The understanding and prediction of such effects and the development of milder and more selective synthetic transformations, applicable to the synthesis of highly complex structures or to the selective chemical modification of proteins, DNA, or even living cells will continue to be the challenge for current and future generations of chemists.

1.3 Hard and Soft Acids and Bases

One of the most useful tools for predicting the outcome of chemical reactions is the principle of hard and soft acids and bases (HSAB), formulated by Pearson in 1963 [13–15]. This principle states that hard acids will react preferentially with hard bases, and soft acids with soft bases, "hard" and "soft" referring to sparsely or highly polarizable reactants. A selection of hard and soft Lewis acids and bases is given in Table 1.1.

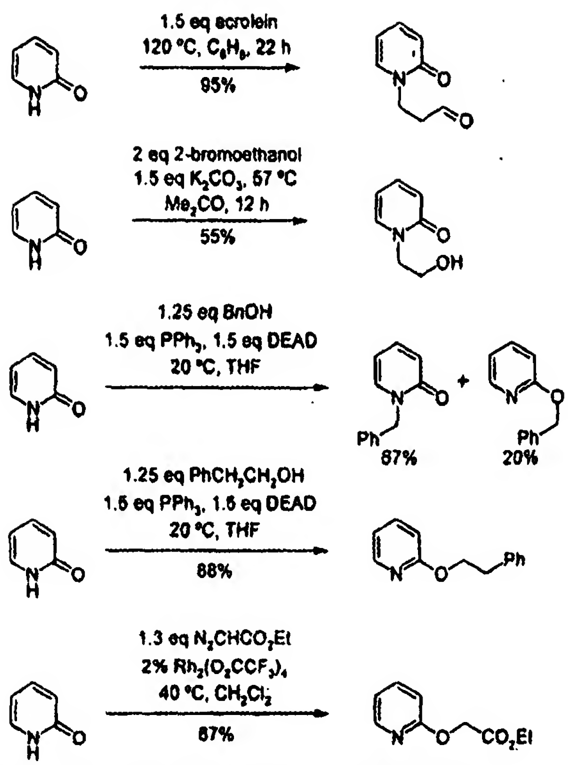
Several chemical observations can be readily explained with the aid of the HSAB principle. For instance, the fact that the early transition metals in high oxidation states, for example titanium(IV), do not usually form complexes with alkenes, carbon monoxide, or phosphines, but form stable oxides instead can be attributed to their hardness. The late transition metals, on the other hand, being highly polarizable, because of their almost completely filled *d* orbitals, readily form complexes with soft bases such as alkenes, carbanions, and phosphines, and these complexes are often unreactive towards water or oxygen. For the same reason, in alkali or early transition metal enolates the metal is usually bound to oxygen, whereas enolates of late transition metals usually contain M–C bonds [17, 18]. While alkali metal alkyls or Grignard reagents react with enones presumably by initial coordination of the metal to oxygen followed by transfer of the alkyl group to the carbonyl carbon atom [16, 19], organocuprates or organopalladium compounds preferentially coordinate and transfer their organic residue to soft C–C double bonds.

Table 1.1. Hard and soft Lewis acids and bases [13, 15, 16] (Z = electron-withdrawing group, M = metal). The acidic or basic centers in molecules are in italics.

Hard acids (non-metals)	**Borderline acids (non-metals)**	**Soft acids (non-metals)**
H^+, $B(OR)_3$, BF_3, BCl_3, RCO^+, CO_2, NC^+, R_3Si^+, Si^{4+}, RPO_2^+, $ROPO_2^+$, As^{3+}, RSO_2^+, $ROSO_2^+$, SO_3, Se^{3+}, Cl^{7+}, I^{7+}, I^{5+}	BR_3, R^+ (softer $CH_3^+ > RCH_2^+ > R_2CH^+ > R_3C^+ >$ vinyl$^+ \approx C_6H_5^+ \approx RC{\equiv}C^+$ harder), RCHO, R_2CO, $R_2C{=}NR$, NO^+, SO_2	BH_3, Ar–Z, C=C–Z, quinones, carbenes, HO^+, RO^+, RS^+, RSe^+, RTe^+, Br_2, Br^+, I_2, I^+
Hard acids (metals)	**Borderline acids (metals)**	**Soft acids (metals)**
Li^+, Na^+, K^+, $BeMe_2$, Be^{2+}, RMgX, Mg^{2+}, Ca^{2+}, Sr^{2+}, $AlCl_3$, $AlMe_3$, AlH_3, $Al(OR)_3$, Al^{3+}, $GaMe_3$, Ga^{3+}, $InMe_3$, In^{3+}, SnR_3^+, $SnMe_2^{2+}$, Sn^{2+}, Sc^{3+}, La^{3+}, $Ti(OR)_4$, Ti^{4+}, Zr^{4+}, VO_2^+, Cr^{3+}, Fe^{3+}, Co^{3+}, Ir^{3+}, Th^{4+}, UO_2^{2+}, Pu^{4+}, Yb^{3+}	GaH_3, $Sn(OR)_4$, $SnCl_4$, Pb^{2+}, Sb^{3+}, Bi^{3+}, $Sc(OTf)_3$, $ScCl_3$, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, RZn^+, Zn^{2+}, $Yb(OTf)_3$, $YbCl_3$	Cs^+, $TlMe_3$, Tl^+, Tl^{3+}, $Pd(PAr_3)_2$, $Pd(PAr_3)_2^{2+}$, Pd^{2+}, Pt^{2+}, Cu^+, Ag^+, Au^+, CdR^+, Cd^{2+}, HgR^+, Hg^+, Hg^{2+}, M^0
Hard bases	**Borderline bases**	**Soft bases**
NH_3, RNH_2, R_2N^-, N_2H_4, H_2O, OH^-, ROH, RO^-, R_2O, RCO_2^-, CO_3^{2-}, NO_3^-, PO_4^{3-}, SO_4^{2-}, ClO_4^-, F^-, Cl^-	AlH_4^-, N_2, N_3^-, $PhNH_2$, R_3N, C_5H_5N, $R_2C{=}NR$, NO_2^-, SO_3^{2-}, Br^-	H^-, BH_4^-, R^- (softer $RC{\equiv}C^- >$ vinyl$^- > R_3C^-$ harder), C_6H_6, $R_2C{=}CR_2$, $RC{\equiv}CR$, CN^-, RNC, CO, PR_3, $P(OR)_3$, AsR_3, RS^-, SCN^-, RSH, R_2S, $S_2O_3^{2-}$, RSe^-, I^-

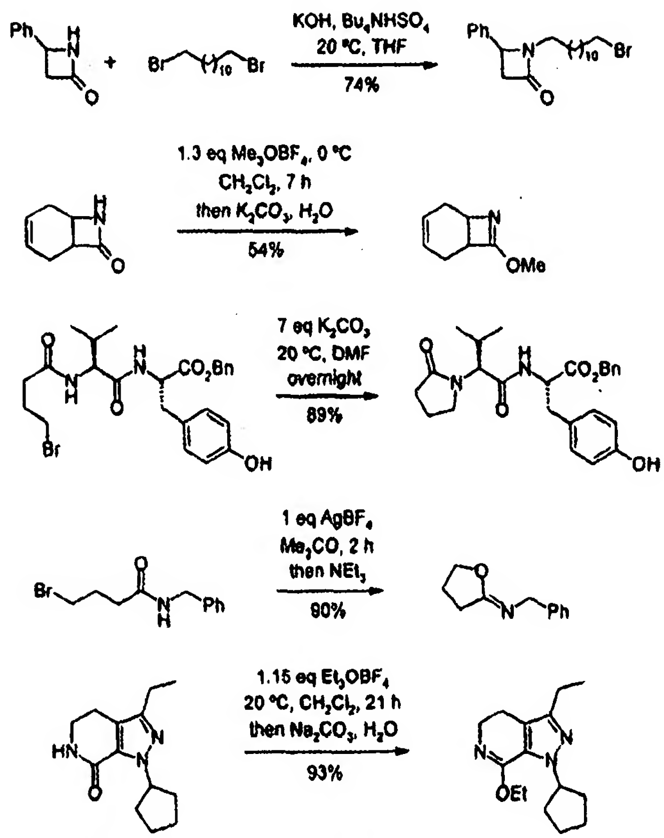
HSAB is particularly useful for assessing the reactivity of ambident nucleophiles or electrophiles, and numerous examples of chemoselective reactions given throughout this book can be explained with the HSAB principle. Hard electrophiles, for example alkyl triflates, alkyl sulfates, trialkyloxonium salts, electron-poor carbenes, or the intermediate alkoxyphosphonium salts formed from alcohols during the Mitsunobu reaction, tend to alkylate ambident nucleophiles at the hardest atom. Amides, enolates, or phenolates, for example, will often be alkylated at oxygen by hard electrophiles whereas softer electrophiles, such as alkyl iodides or electron-poor alkenes, will preferentially attack amides at nitrogen and enolates at carbon.

2-Pyridone is *O*-alkylated more readily than normal amides, because the resulting products are aromatic. With soft electrophiles, however, clean *N*-alkylations can be performed (Scheme 1.7). The Mitsunobu reaction, on the other hand, leads either to mixtures of *N*- and *O*-alkylated products or to *O*-alkylation exclusively, probably because of the hard, carbocation-like character of the intermediate alkoxyphosphonium cations. Electrophilic rhodium carbene complexes also preferentially alkylate the oxygen atom of 2-pyridone or other lactams [20] (Scheme 1.7).



Scheme 1.7. Regioselective alkylation of 2-pyridone [20–22].

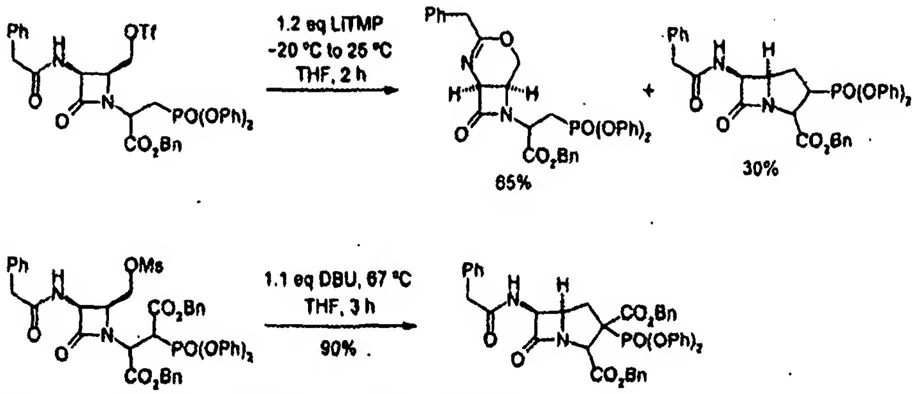
Lactams and some non-cyclic, secondary amides (RCONHR) can be alkylated with high regioselectivity either at nitrogen (Section 6.6) or at oxygen. *N*-Alkylations are generally conducted under basic reaction conditions whereas *O*-alkylations are often performed with trialkyloxonium salts, dialkyl sulfates, or alkyl halides/silver salts without addition of bases. Protonated imino ethers are formed; these are usually not isolated but are converted into the free imino ethers with aqueous base during the work-up. Scheme 1.8 shows examples of the selective alkylation of lactams and of the formation of 2-pyrrolidinones or 2-iminotetrahydrofurans by cyclization of 4-bromobutyramides.



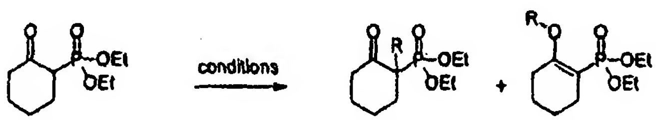
Scheme 1.8. Regioselective alkylation of amides [23–27].

The triflate sketched in Scheme 1.9 mainly alkylates the amide at oxygen, instead of alkylating the softer, lithiated phosphonate. Selective C-alkylation can be achieved in this instance by choosing a less reactive mesylate as electrophile and by enhancing the acidity of the phosphonate.

The regioselectivity of the alkylation of enolates can also be controlled by the hardness of the alkylating agent [29]. As illustrated by the examples in Scheme 1.10, allyl, propargyl, or alkyl bromides or iodides mainly yield C-alkylated products, whereas the harder sulfonates preferentially alkylate at oxygen.



Scheme 1.9. Intramolecular alkylation of amides and phosphonates [28].



Bu_4NHSO_4, NaOH CH_2Cl_2, 40 °C, 24 h	2.2 eq 	54%	12%
	2.2 eq 	84%	8%
	2.2 eq MeI	82%	9%
	2.2 eq EtI	44%	33%
KH, 20 °C DMSO, 40 h	1.1 eq MeOTs	4%	62%

Scheme 1.10. Regioselective alkylation of enolates [30, 31].

1.4
The Curtin–Hammett Principle

In the 1940s the idea was prevalent among chemists that the conformation of a reactant could be determined from the structure of a reaction product, i.e. the major conformer would yield the major product. This assumption was shown to be incorrect by Curtin and Hammett in the 1950s [32].

For a reaction in which a starting material A is an equilibrium mixture of two conformers (or diastereomers, tautomers, rotamers, etc.) A^1 and A^2 (Eq. 1.1), two extreme situations can be considered – one in which equilibration of A^1 and A^2 is slow if compared with their reaction with B ($k^1, k^2 \ll k^C, k^D$), and one in which equilibration of A^1 and A^2 is much faster than their reaction with B ($k^1, k^2 \gg k^C, k^D$).

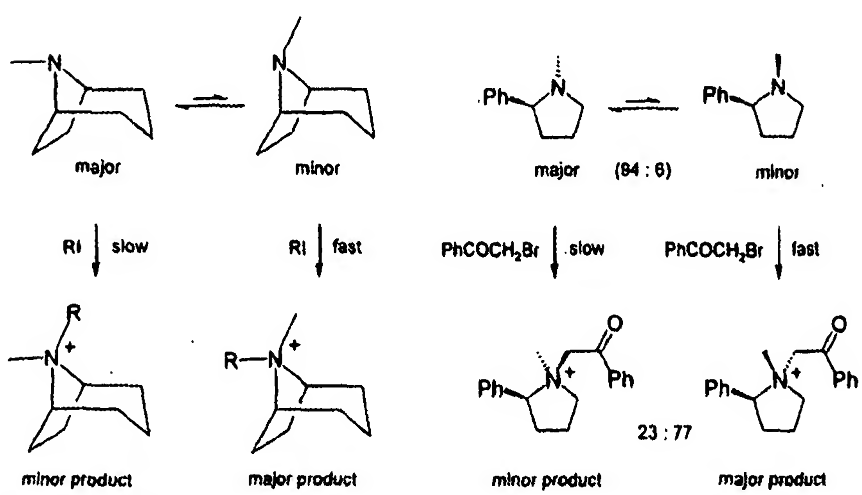
$$C \xleftarrow[k^C]{B} A^1 \underset{k^1}{\overset{k^2}{\rightleftharpoons}} A^2 \xrightarrow[k^D]{B} D \qquad \text{(Eq. 1.1)}$$

If equilibration of A^1 and A^2 is slow, the product ratio [C]/[D] will be equal to the ratio of conformers of the starting material A ($[A^1]/[A^2]$) and independent of the ratio k^C/k^D. If equilibration is rapid, however, the amount of C and D formed will depend both on the ratio of starting materials ($[A^1]/[A^2]$) and on the ratio of the two reaction rate constants k^C and k^D: $[D]/[C] = [A^2]/[A^1] \times k^D/k^C$ [32].

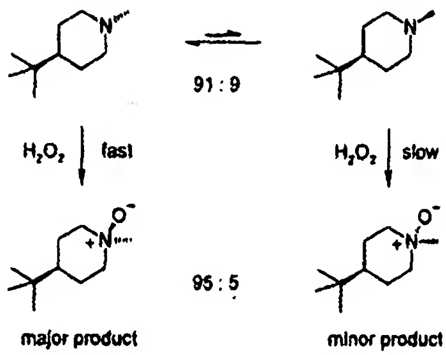
The main implication of these derivations is that if equilibration is rapid, the product ratio cannot always be intuitively predicted if the reaction rates k^C and k^D are unknown. Because energy-rich conformers, present in low concentrations only, are often more reactive than more stable conformers, it is not unusual for the main product of a reaction to result from a minor conformer which cannot even be observed.

Two examples of such situations are sketched in Scheme 1.11. Quaternization of tropane occurs mainly from the less hindered "pyrrolidine side" (equatorial attack at the piperidine ring), even though the main conformer of tropane has an equatorial methyl group. Similarly, 1-methyl-2-phenylpyrrolidine yields mainly an *anti* alkylated product via alkylation of the minor *cis* conformer when treated with phenacyl bromide [33]. In both instances the less stable conformer is more reactive to such an extent that the major product of the reaction results from this minor conformer. A further notable example of a reaction in which the main product results from a minor but more reactive intermediate is the enantioselective hydrogenation of α-acetamidocinnamates with a chiral rhodium-based catalyst [34].

This does, however, not need to be so. Oxidation of 1-methyl-4-*tert*-butylpiperidine, for example, yields mainly the amine *N*-oxide derived from the most stable conformer (Scheme 1.12). In this example the more energy-rich (less stable) conformer reacts more slowly than the major conformer.



Scheme 1.11. Diastereoselective quaternization of tertiary amines [32, 33, 35].



Scheme 1.12. Diastereoselective oxidation of 4-*tert*-butyl-1-methylpiperidine [32, 36, 37].

To conclude, the Curtin–Hammett principle states that the relative amounts of products formed from two interconverting conformers depend on the reactivity of these two conformers if the interconversion of these conformers is rapid, and cannot always be intuitively predicted.

References

1 Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

2 Evans, D. A.; Barnes, D. M. Cationic bis(oxazoline)Cu(II) Lewis acid catalysts. Enantioselective furan Diels–Alder reaction in the synthesis of *ent*-shikimic acid. *Tetrahedron Lett.* 1997, *38*, 57–58.

3 Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. Total synthesis of lycopodium alkaloids: (±)-lycopodine, (±)-lycodine, and (±)-lycodoline. *J. Am. Chem. Soc.* 1982, *104*, 1054–1068.

4 Oplinger, J. A.; Paquette, L. A. Synthesis of the forskolin skeleton via anionic oxy-Cope rearrangement. *Tetrahedron Lett.* 1987, *28*, 5441–5444.

5 Bérubé, G.; Fallis, A. G. An intramolecular cycloaddition-sigmatropic rearrangement approach to (±) gascardic acid. *Tetrahedron Lett.* 1989, *30*, 4045–4048.

6 Paquette, L. A.; Romine, J. L.; Lin, H.-S. Diastereoselective π-facially controlled nucleophilic additions of chiral vinylorganometallics to chiral β,γ-unsaturated ketones. 2. A practical method for stereocontrolled elaboration of the decahydro-*as*-indacene subunit of ikarugamycin. *Tetrahedron Lett.* 1987, *28*, 31–34.

7 Paquette, L. A.; Zhao, M. Enantiospecific total synthesis of natural (+)-taxusin. 1. Retrosynthesis, advancement to diastereomeric *trans*-$\Delta^{9,10}$-tricyclic olefinic intermediates, and the stereocontrol attainable because of intrinsic rotational barriers therein. *J. Am. Chem. Soc.* 1998, *120*, 5203–5212.

8 Maleczka, R. E.; Paquette, L. A. Adaptation of oxyanionic sigmatropy to the convergent enantioselective synthesis of ambergris-type odorants. *J. Org. Chem.* 1991, *56*, 6538–6546.

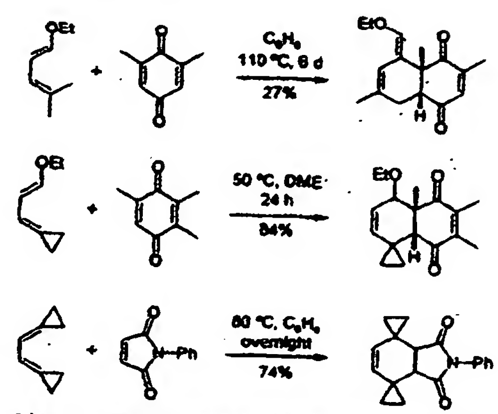
9 MacDougall, J. M.; Santora, V. J.; Verma, S. K.; Turnbull, P.; Hernandez, C. R.; Moore, H. W. Cyclobutenone-based syntheses of polyquinanes and bicyclo[6.3.0]undecanes by tandem anionic oxy-Cope reactions. Total synthesis of (±)-precapnelladiene. *J. Org. Chem.* 1998, *63*, 6905–6913.

10 Polniaszek, R. P.; Dillard, L. W. Stereospecific total synthesis of decahydroquinoline alkaloids (±)-195A and (±)-2-*epi*-195A. *J. Org. Chem.* 1992, *57*, 4103–4110.

11 Sierra, M. A.; de la Torre, M. C. Dead ends and detours en route to total syntheses of the 1990s. *Angew. Chem. Int. Ed.* 2000, *39*, 1538–1559.

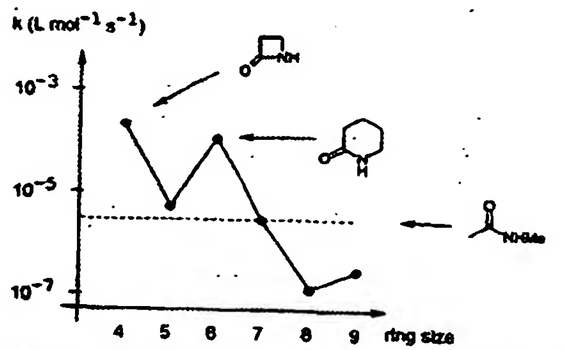
12 Crimmins, M. T.; Dudek, C. M.; Cheung, W.-H. A fragmentation–rearrangement sequence of cyclobutylcarbinyl radicals. *Tetrahedron Lett.* 1992, *33*, 181–184.

13 Pearson, R. G. *Chemical Hardness*; Wiley-VCH: Weinheim, 1997.
14 Ho, T.-L. The hard soft acids bases (HSAB) principle and organic chemistry. *Chem. Rev.* 1975, *75*, 1–20.
15 Woodward, S. HSAB matching and mismatching in selective catalysis and synthesis. *Tetrahedron* 2002, *58*, 1017–1050.
16 March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1992.
17 Albanese, J. A.; Staley, D. L.; Rheingold, A. L.; Burmeister, J. L. Synthesis and molecular structure of a dinuclear phosphorus ylide complex: μ-dichlorobis[chloro(benzoylmethylenetri-*n*-butylphosphorane)palladium(II)]. *J. Organomet. Chem.* 1989, *375*, 265–272.
18 Culkin, D. A.; Hartwig, J. F. C–C Bond forming reductive elimination of ketones, esters, and amides from isolated arylpalladium(II) enolates. *J. Am. Chem. Soc.* 2001, *123*, 5816–5817.
19 Hoffmann, R. W.; Hölzer, B. Concerted and stepwise Grignard additions, probed with a chiral Grignard reagent. *Chem. Commun.* 2001, 491–492.
20 Busch-Petersen, J.; Corey, E. J. A Rh(II) catalytic approach to the synthesis of ethers of a minor component in a tautomeric set. *Org. Lett.* 2000, *2*, 1641–1643.
21 Somekawa, K.; Okuhira, H.; Sendayama, M.; Suishu, T.; Shimo, T. Intramolecular [2 + 2] photocycloadditions of 1-(ω-alkenyl)-2-pyridones possessing an ester group on the olefinic carbon chain. *J. Org. Chem.* 1992, *57*, 5708–5712.
22 Comins, D. L.; Jianhua, G. *N*- vs *O*-Alkylation in the Mitsunobu reaction of 2-pyridone. *Tetrahedron Lett.* 1994, *35*, 2819–2822.
23 Crombie, L.; Jones, R. C. F.; Haigh, D. Transamidation reactions of β-lactams: a synthesis of (±)-dihydroperiphylline. *Tetrahedron Lett.* 1986, *27*, 5151–5154.
24 Paquette, L. A.; Kakihana, T.; Hansen, J. F.; Philips, J. C. π-Equivalent heterocyclic congeners of cyclooctatetraene. The synthesis and valence isomerization of 2-alkoxyazocines. *J. Am. Chem. Soc.* 1971, *93*, 152–161.
25 Reid, R. C.; Kelso, M. J.; Scanlon, M. J.; Fairlie, D. P. Conformationally constrained macrocycles that mimic tripeptide β-strands in water and aprotic solvents. *J. Am. Chem. Soc.* 2002, *124*, 5673–5683.
26 Alanine, A. I. D.; Fishwick, C. W. G.; Szantay, C. Facile preparation of 2-imino tetrahydrofurans, pyrans and oxepans. *Tetrahedron Lett.* 1989, *30*, 6571–6572.
27 Urban, F. J.; Anderson, B. G.; Orrill, S. L.; Daniels, P. J. Process research and large-scale synthesis of a novel 5,6-dihydro-(9*H*)-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine PDE-IV inhibitor. *Org. Process Res. Dev.* 2001, *5*, 575–580.
28 Hakimelahi, G. H.; Moosavi-Movahedi, A. A.; Tsay, S.-C.; Tsai, F.-Y.; Wright, J. D.; Dudev, T.; Hakimelahi, S.; Lim, C. Design, synthesis, and SAR of novel carbapenem antibiotics with high stability to xanthomonas maltophilia oxyiminocephalosporinase type II. *J. Med. Chem.* 2000, *43*, 3632–3640.
29 Damoun, S.; Van de Woude, G.; Choho, K.; Geerlings, P. Influence of alkylating reagent softness on the regioselectivity in enolate ion alkylation: a theoretical local hard and soft acids and bases study. *J. Phys. Chem. A* 1999, *103*, 7861–7866.
30 Ruder, S. M.; Kulkarni, V. R. Phase transfer catalyzed alkylation of 2-(diethoxyphosphinyl)-cyclohexanone. *Synthesis* 1993, 945–947.
31 Ruder, S. M.; Ding, M. [2 + 2] Cycloaddition of cyclic vinyl phosphonates with ketenes. *J. Chem. Soc. Perkin Trans. 1* 2000, 1771–1776.
32 Seeman, J. I. Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin–Hammett/Winstein–Holness kinetics. *Chem. Rev.* 1983, *83*, 83–134.
33 Solladié-Cavallo, A.; Solladié, G. Etude de la stéréosélectivité de la quaternisation de pyrrolidines-1,2 disubstituées. *Tetrahedron Lett.* 1972, 4237–4240.
34 Halpern, J. Mechanism and stereoselectivity of asymmetric hydrogenation. *Science* 1982, *217*, 401–407.
35 Seeman, J. I.; Secor, H. V.; Hartung, H.; Galzerano, R. Steric effects in conformationally mobile systems. The methylation of 1-methyl-2-arylpyrrolidines related to nicotine. *J. Am. Chem. Soc.* 1980, *102*, 7741–7747.
36 Shvo, Y.; Kaufman, E. D. Configurational and conformational analysis of cyclic amine oxides. *Tetrahedron* 1972, *28*, 573–580.
37 Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. Conformational effects in compounds with 6-membered rings XII. The conformational equilibrium in *N*-methylpiperidine. *Tetrahedron* 1977, *33*, 915–925.



Scheme 3.7. Diels–Alder reactions with cyclopropylidenes [22–24].

ring scission. Eight- and nine-membered lactams are more resistant to nucleophilic hydrolysis than non-cyclic amides; this might be because of an increase in transannular repulsive van der Waals interactions during the addition of hydroxide to these amides.

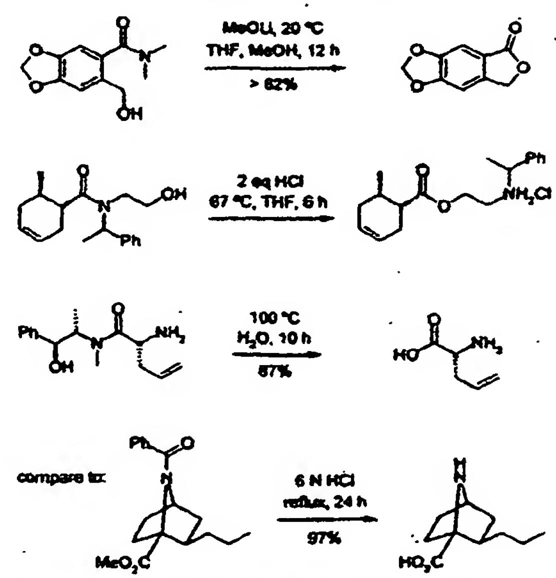


Scheme 3.8. Rates of lactam hydrolysis with aqueous base [25]. For comparison, the rate of hydrolysis of *N*-methylacetamide is shown.

3.3 Incompatible Functional Groups

It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly. For instance, many phthalic acid, maleic acid, or 2-(hydroxymethyl)benzoic acid derivatives are notoriously sensitive because of the close proximity of the two functional groups (Scheme 3.9). Similarly, amides of 2-aminoethanols rearrange readily to esters under acidic reaction conditions [26] and undergo hydrolysis under mildly basic conditions, mainly because the hydroxyl group is close to the amide bond (Scheme 3.9). Normal amides usually require treatment with highly concentrated mineral acids at high temperatures to undergo hydrolysis (last example, Scheme 3.9).

Mannich bases (2-aminoethyl ketones) are another class of inherently unstable compounds which often undergo facile thermal elimination of the amine to yield a vinyl ketone [30]. Chemically related to Mannich bases are 2- or 4-(aminomethyl)-



Scheme 3.9. Hydrolysis of amides with and without intramolecular assistance [26–29].

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

26164 7590 03/25/2008

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/25/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,545	05/16/2006	Andrew Baxter	06275-510US1 101279-1P US	3967

TITLE OF INVENTION: NOVEL COMPOUNDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	06/25/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26164 7590 03/25/2008

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,545	05/16/2006	Andrew Baxter	06275-510US1 101279-1P US	3967

TITLE OF INVENTION: NOVEL COMPOUNDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	06/25/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
AULAKH, CHARANJIT	1625	514-278000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
   - ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
   (1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
   (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
   1 ______
   2 ______
   3 ______

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies ______

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number ______ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature ______ Date ______

Typed or printed name ______ Registration No. ______

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,545	05/16/2006	Andrew Baxter	06275-510US1 101279-1P US	3967

26164 7590 03/25/2008

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 03/25/2008

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 253 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 253 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	**Application No.** 10/579,545	**Applicant(s)** BAXTER ET AL.	
	Examiner Charanjit S. Aulakh	**Art Unit** 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☒ The allowed claim(s) is/are 1-11.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/16/06, 3/9/07
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date 3/20/08 .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

1. According to a preliminary amendment filed on May 16, 2005, the applicants have canceled claim 12 and furthermore, have amended claims 3-6, 10, 11 and 13-19.

2. Claims 1-11 and 13-19 are now pending in the application.

EXAMINER'S AMENDMENT

3. The following amendment is pursuant to a telephone conversation with the applicant's attorney, Mr. John Kendall on March 20, 2008. The following changes have been made in claims and specification:

Cancel claims 13-19 without prejudice.

In claim 1, page 4, last line, after salt, delete ---- or solvate -----.

In claim 8, page 11, line 1, after salts, delete ---- and solvates -----.

In claim 9, page 11, line 2, after salt, delete ---- or solvate ----- and furthermore, on page 13, last line, after salt, delete ---- or solvate -----.

In claim 10, page 13, line 2, after salt, delete ---- or solvate -----.

In claim 11, page 13, lines 2-3, after salt, delete ---- or solvate ----- and furthermore, in line 5, after salt, delete ---- or solvate -----.

In the specification, insert the enclosed abstract as the last page which is copied from the corresponding WO application.

REASONS FOR ALLOWANCE

4. The following is an examiner's statement of reasons for allowance:

Claims 1-11 are allowed since the instant compounds of formula (I) and pharmaceutical composition containing these compounds are neither disclosed nor obvious over the prior art. In the art, Hossain (WO 2004/005295, cited on applicant's form 1449) discloses novel tricyclic spiropiperidines or spiropyrrolidines of formula (I) which are closely related to the instant compounds (see page 2, lines 1-24). However, the compounds of Hussain differ from the instant compounds by having different value of variable R3 on the phenyl ring.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Charanjit S. Aulakh/
Primary Examiner, Art Unit 1625

Interview Summary	Application No. 10/579,545	Applicant(s) BAXTER ET AL.	
	Examiner Charanjit S. Aulakh	Art Unit 1625	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Charanjit S. Aulakh*. (3)_____.

(2) *John kendall*. (4)_____.

Date of Interview: *20 March 2008*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *1,8-11 and 13-19*.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

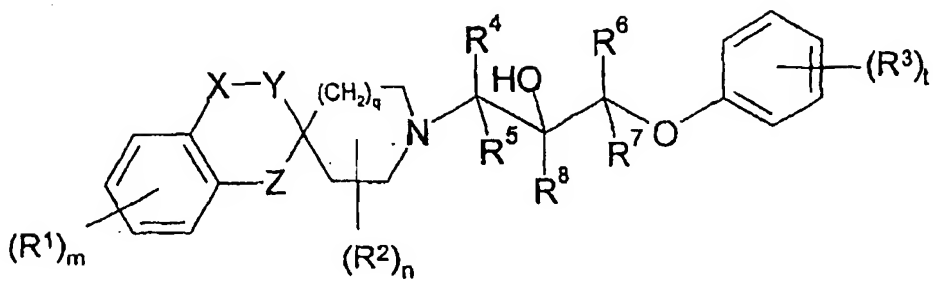
Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *An agreement was reached to cancel claims 13-19 and furthermore, to amend claims 1 and 8-11 by an examiner's amendment*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Charanjit S. Aulakh/
Primary Examiner, Art Unit 1625
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.



(I)

Abstract: The invention provides compounds of formula (I) wherein m, R^1, n, R^2, q, X, Y, Z, t, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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=> d ibib abs hitstr 1-7

L4   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2005:371060  CAPLUS
DOCUMENT NUMBER:         142:406026
TITLE:                   Preparation of insecticidal N-substituted azacycles
INVENTOR(S):             Theodoridis, George; Rosen, David; Zhang, Shunxiang;
                         Yeager, Walter H.; Henrie, Robert N., II; Ahmed, Syed
                         Z.; Men, Hongbin; Donovan, Stephen F.
PATENT ASSIGNEE(S):      FMC Corporation, USA
SOURCE:                  PCT Int. Appl., 113 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.        DATE
     ---------------     ----   --------   --------------------   --------
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     WO 2005036961        A3    20050811
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             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
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     CN 1867330           A     20061122   CN 2004-80029607       20041004
     BR 2004015073        A     20061128   BR 2004-15073          20041004
     JP 2007508306        T     20070405   JP 2006-534244         20041004
     WO 2006031674        A1    20060323   WO 2005-US32279        20050912
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             SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
             ZA, ZM, ZW
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     IN 2006DN01806       A     20070810   IN 2006-DN1806         20060403
     MX 2006PA03860       A     20060703   MX 2006-PA3860         20060406
     IN 2007DN01858       A     20070427   IN 2007-DN1858         20070309
     KR 2007106678        A     20071105   KR 2007-707882         20070406
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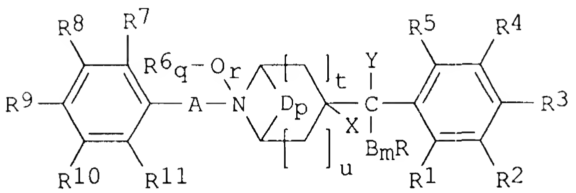
IN 2007DN02686	A	20070817	IN 2007-DN2686		20070411
US 2008039631	A1	20080214	US 2007-662598		20070718
PRIORITY APPLN. INFO.:			US 2003-510568P	P	20031010
			US 2004-609533P	P	20040913
			WO 2004-US32720	W	20041004
			WO 2005-US32279	W	20050912

OTHER SOURCE(S): CASREACT 142:406026; MARPAT 142:406026

GI



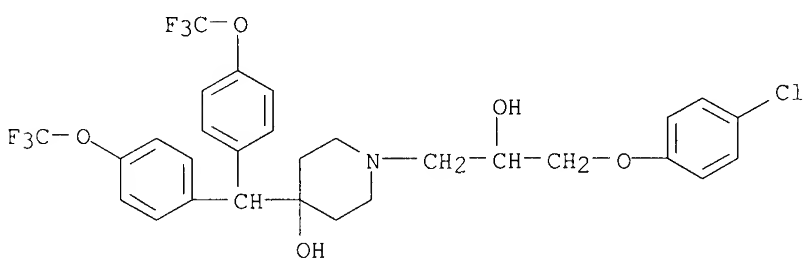
I

AB N-substituted azacycle derivs. I [m, q, r, t, u = 0 or 1; p = 0, 1, 2, or 3; A = CH2, CH2CH2, NCH2CH2, OCH2CH2, etc.; B = O, S, CH2O, etc.; D = CH2; X = halo, OH, (halo)alkyl, hydroxyalkyl, alkoxy, etc.; Y = H, halo, (halo)alkyl, etc.; XCCY = 1,3-dioxolane; R, R1, R2, R3, R4, R5 = H, halo, (halo)alkyl, OH, hydroxyalkyl, etc.; R6, R7, R8, R9, R10, R11 = H, halo, OH, (hydroxy)alkyl, alkoxy, etc.] are prepared as insecticides.

IT 850227-27-9P 850227-28-0P 850227-29-1P
RL: AGR (Agricultural use); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation as insecticide)

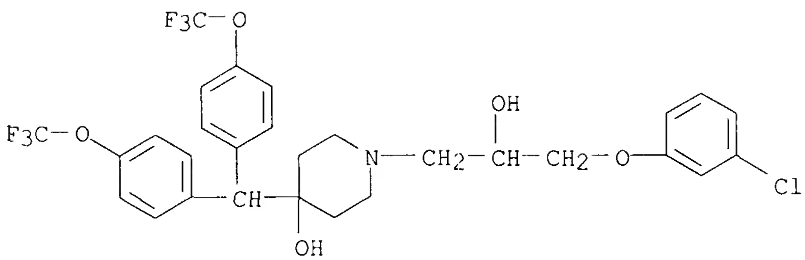
RN 850227-27-9 CAPLUS

CN 1-Piperidineethanol, 4-[bis[4-(trifluoromethoxy)phenyl]methyl]-α-[(4-chlorophenoxy)methyl]-4-hydroxy- (CA INDEX NAME)

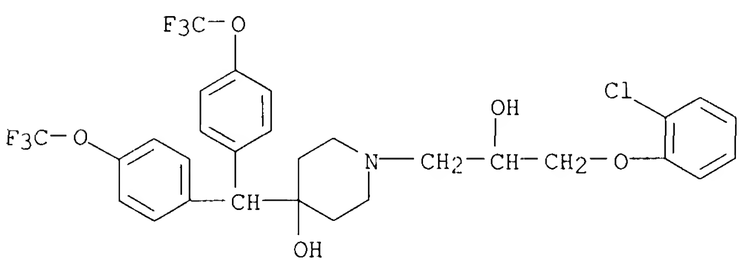


RN 850227-28-0 CAPLUS

CN 1-Piperidineethanol, 4-[bis[4-(trifluoromethoxy)phenyl]methyl]-α-[(3-chlorophenoxy)methyl]-4-hydroxy- (CA INDEX NAME)



RN 850227-29-1 CAPLUS
CN 1-Piperidineethanol, 4-[bis[4-(trifluoromethoxy)phenyl]methyl]-α-[(2-chlorophenoxy)methyl]-4-hydroxy- (CA INDEX NAME)



L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2000:900636 CAPLUS
DOCUMENT NUMBER:	134:42151
TITLE:	Preparation of new bispidines useful in the treatment of cardiac arrhythmias
INVENTOR(S):	Bjore, Annika; Bjorsne, Magnus; Halvarsson, Torbjorn; Hoffmann, Kurt-jurgen; Samuelsson, Bertil; Strandlund, Gert
PATENT ASSIGNEE(S):	Astrazeneca Ab, Swed.
SOURCE:	PCT Int. Appl., 87 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000076999	A1	20001221	WO 2000-SE1253	20000615

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

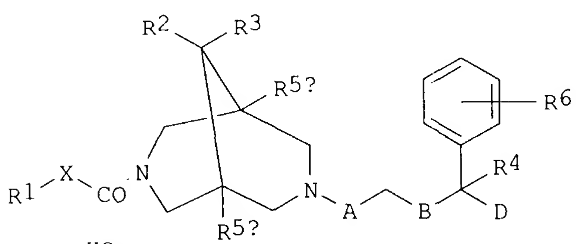
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2384339	A1	20001221	CA 2000-2384339	20000615
BR 2000011673	A	20020312	BR 2000-11673	20000615
EP 1192154	A1	20020403	EP 2000-944526	20000615

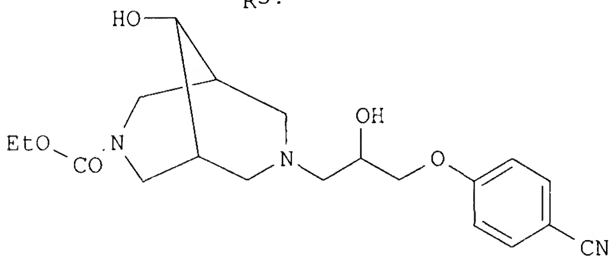
EP 1192154	B1	20040317			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200103659	T2	20020422	TR 2001-3659		20000615
JP 2003502328	T	20030121	JP 2001-503857		20000615
EE 200100674	A	20030217	EE 2001-674		20000615
HU 2002002929	A2	20030228	HU 2002-2929		20000615
HU 2002002929	A3	20030428			
AU 762244	B2	20030619	AU 2000-58611		20000615
NZ 516015	A	20030630	NZ 2000-516015		20000615
AT 261965	T	20040415	AT 2000-944526		20000615
PT 1192154	T	20040730	PT 2000-944526		20000615
ES 2216912	T3	20041101	ES 2000-944526		20000615
US 6887881	B1	20050503	US 2000-623709		20000615
ZA 2001009800	A	20030228	ZA 2001-9800		20011128
IN 2001MN01520	A	20050304	IN 2001-MN1520		20011203
MX 2001PA12925	A	20020730	MX 2001-PA12925		20011213
NO 2001006127	A	20020212	NO 2001-6127		20011214
PRIORITY APPLN. INFO.:			SE 1999-2270	A	19990616
			WO 2000-SE1253	W	20000615

OTHER SOURCE(S): MARPAT 134:42151

GI



I



II

AB Bispidines, such as I [R1 = alkyl, arylalkyl, etc.; R2, R3 = H, OH, alkyl, etc.; R2R3 = O; R4, R5a, R5b = H, alkyl; R6 = OH, CN, NO2, NH2, halogen, etc.; X = O, S; A, B = bond, linking group, such as alkylene, etc.; D = H, OH, alkyl, aminoalkyl, etc.], were prepared for pharmaceutical use in the treatment of cardiac arrhythmias, in particular atrial and ventricular arrhythmias. Thus, bispidine II was prepared in multistep synthetic sequence starting from Et 4-oxo-1-piperidinecarboxylate, epichlorohydrin, and 4-cyanophenol. The prepared bispidines were tested for primary electrophysiol. effects in anesthetized guinea pigs.

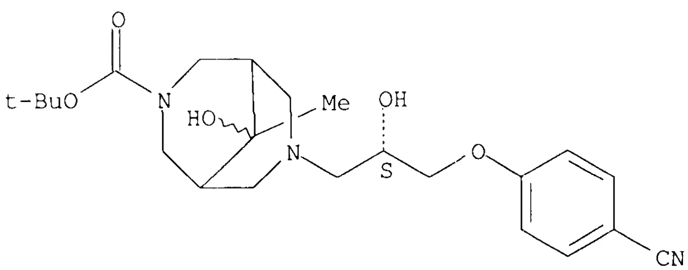
IT 313269-44-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of new bispidines useful in the treatment of cardiac arrhythmias)

RN 313269-44-2 CAPLUS
CN 3,7-Diazabicyclo[3.3.1]nonane-3-carboxylic acid, 7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-hydroxy-9-methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

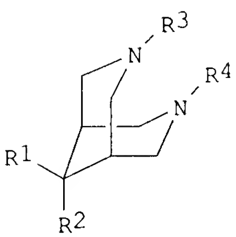
L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:404964 CAPLUS
DOCUMENT NUMBER: 131:58860
TITLE: Preparation of 3,7-diazabicyclo[3.3.1]nonane-3-carboxylates as antiarrhythmic agents
INVENTOR(S): Strandlund, Gert; Alstermark, Christer; Bjore, Annika; Bjorsne, Magnus; Frantsi, Marianne; Halvarsson, Torbjorn; Hoffmann, Kurt-Jurgen; Lindstedt, Eva-Lotte; Polla, Magnus
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9931100	A1	19990624	WO 1998-SE2276	19981210
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9811130	A	19990617	ZA 1998-11130	19981204
CA 2314490	A1	19990624	CA 1998-2314490	19981210
AU 9917953	A	19990705	AU 1999-17953	19981210
TR 200001757	T2	20000921	TR 2000-1757	19981210
BR 9813668	A	20001017	BR 1998-13668	19981210
EP 1047695	A1	20001102	EP 1998-962796	19981210
EP 1047695	B1	20040317		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EE 200000365	A	20011015	EE 2000-365	19981210

HU 2001002307	A2	20011228	HU 2001-2307		19981210
HU 2001002307	A3	20020228			
JP 2002508375	T	20020319	JP 2000-539024		19981210
AT 261964	T	20040415	AT 1998-962796		19981210
PT 1047695	T	20040730	PT 1998-962796		19981210
ES 2216337	T3	20041016	ES 1998-962796		19981210
US 6291475	B1	20010918	US 1999-214756		19990112
MX 2000PA05600	A	20011031	MX 2000-PA5600		20000607
NO 2000003137	A	20000817	NO 2000-3137		20000616
PRIORITY APPLN. INFO.:			SE 1997-4709	A	19971217
			WO 1998-SE2276	W	19981210

OTHER SOURCE(S): MARPAT 131:58860

GI



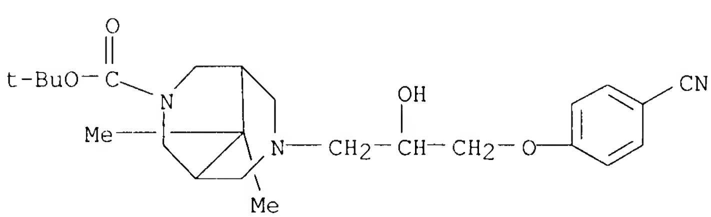
I

AB Title compds. [I; R1,R2 = H or alkyl; R1R2 = OCH2CH2O, (CH2)4-5; R3 = CCR10R11AR; A = bond, alkylene, (CH2)nZ, CONR20, etc.; B = bond, alkylene, NR23(CH2)r, O(CH2)r; R = (un)substituted Ph; R4 = COXR9; R9 = alkyl, (un)substituted phenyl(alkyl), -naphthyl; R10 = H or OH; R11,R20,R23 = H or alkyl; X = O or S; Z = NR20, SO0-2, O; n,r = 0-4] were prepared Thus, 4-(NC)C6H4OH was condensed with epichlorohydrin and the product aminated by I (R1 = R2 = H, R4 = CO2CMe3)(II; R3 = H)(preparation given) to give II [R3 = CH2CH(OH)CH2OC6H4(CN)-4]. Data for biol. activity of I were given.

IT 227940-56-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3,7-diazabicyclo[3.3.1]nonane-3-carboxylates as antiarrhythmic agents)

RN 227940-56-9 CAPLUS

CN 3,7-Diazabicyclo[3.3.1]nonane-3-carboxylic acid, 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-9,9-dimethyl-, 1,1-dimethylethyl ester (CA INDEX NAME)



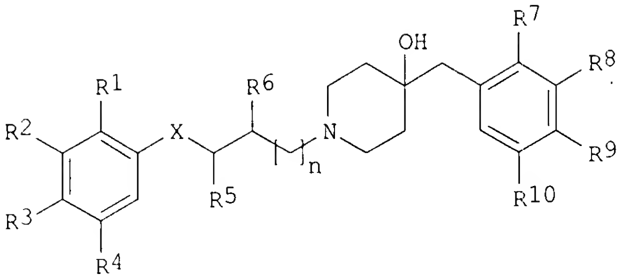
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:221773 CAPLUS
DOCUMENT NUMBER: 130:281992
TITLE: Preparation of 4-hydroxypiperidines as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers
INVENTOR(S): Alanine, Alexander; Buttelmann, Bernd; Neidhart, Marie-paule Heitz; Pinard, Emmanuel; Wyler, Rene
PATENT ASSIGNEE(S): Hoffmann-La Roche Inc., USA
SOURCE: U.S., 20 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 5889026	A	19990330	US 1997-891781		19970714
TW 498067	B	20020811	TW 1997-86108797		19970624
IN 1997MA01505	A	20050304	IN 1997-MA1505		19970707
EP 824098	A1	19980218	EP 1997-111742		19970710
EP 824098	B1	20011031			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
AT 207899	T	20011115	AT 1997-111742		19970710
ES 2164967	T3	20020301	ES 1997-111742		19970710
PT 824098	T	20020429	PT 1997-111742		19970710
CA 2210044	A1	19980119	CA 1997-2210044		19970714
CA 2210044	C	20060214			
ZA 9706224	A	19980119	ZA 1997-6224		19970714
HU 9701194	A2	19990528	HU 1997-1194		19970714
HU 9701194	A3	19990628			
IL 121299	A	20011223	IL 1997-121299		19970714
JP 10067742	A	19980310	JP 1997-192173		19970717
JP 3179050	B2	20010625			
CZ 290898	B6	20021113	CZ 1997-2274		19970717
NO 9703337	A	19980120	NO 1997-3337		19970718
NO 308657	B1	20001009			
CN 1171396	A	19980128	CN 1997-114707		19970718
CN 1120154	B	20030903			
AU 9728756	A	19980129	AU 1997-28756		19970718
AU 719352	B2	20000504			
RU 2178412	C2	20020120	RU 1997-113374		19970718
BR 9704031	A	19981229	BR 1997-4031		19970721
KR 235804	B1	19991215	KR 1997-34233		19970722
HU 9702315	A2	19990628	HU 1997-2315		19971201
HU 9702315	A3	20000928			
HK 1009124	A1	20020906	HK 1998-109919		19980813
PRIORITY APPLN. INFO.:			EP 1996-111660	A	19960719
			EP 1997-105366	A	19970401
			EP 1996-119345	A	19961203
			EP 1997-111742	A	19970710

OTHER SOURCE(S): MARPAT 130:281992
GI



I

AB The title compds. [I; X = O, NH, CH2, etc.; R1-R4 = H, halo, OH, etc.; R5, R6 = H, alkyl, OH, etc.; R7-R10 = H, alkyl, halo, etc.; n = 0-1] and their pharmaceutically acceptable acid addition salts, useful as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers, were prepared and formulated. Thus, hydrogenation of (RS)-1-[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]-4-(4-methylbenzyl)piperidin-4-ol in the presence of Pd/C in EtOH afforded 58% I [X = O; R1, R2, R4 = H; R3 = OH; R5 = H; R6 = OH; n = 1; R7, R8, R10 = H; R9 = Me] which showed IC50 of 0.015 μM in 3H-Ro 25-6981 binding expts.

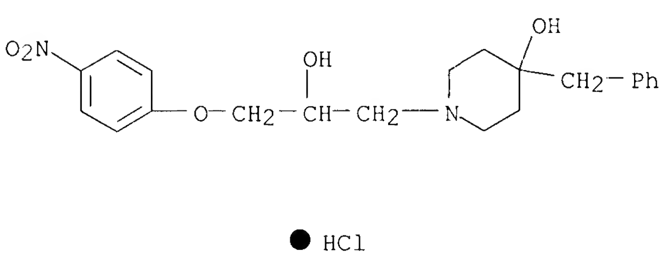
IT 222421-37-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 4-hydroxypiperidines as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers)

RN 222421-37-6 CAPLUS

CN 1-Piperidineethanol, 4-hydroxy-α-[(4-nitrophenoxy)methyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



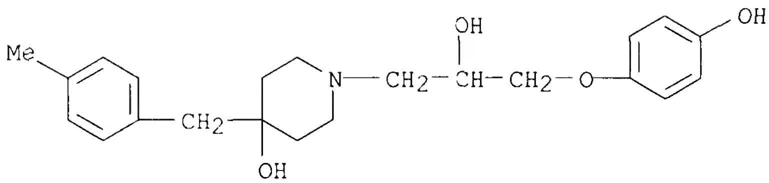
IT 222421-29-6P 222421-31-0P 222421-33-2P
222421-34-3P 222421-36-5P 222421-39-8P
222421-51-4P 222421-53-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 4-hydroxypiperidines as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers)

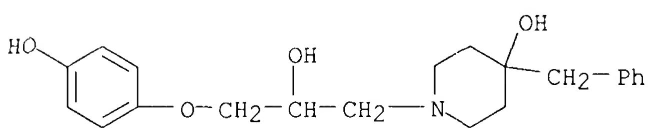
RN 222421-29-6 CAPLUS

CN 1-Piperidineethanol, 4-hydroxy-α-[(4-hydroxyphenoxy)methyl]-4-[(4-methylphenyl)methyl]-, hydrochloride (9CI) (CA INDEX NAME)



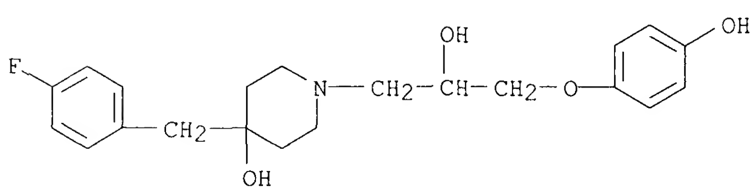
● HCl

RN 222421-31-0 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[(4-hydroxyphenoxy)methyl]-4-(phenylmethyl)-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

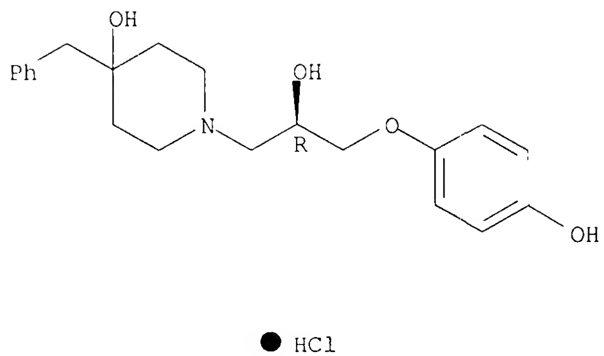
RN 222421-33-2 CAPLUS
CN 1-Piperidineethanol, 4-[(4-fluorophenyl)methyl]-4-hydroxy-α-[(4-hydroxyphenoxy)methyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

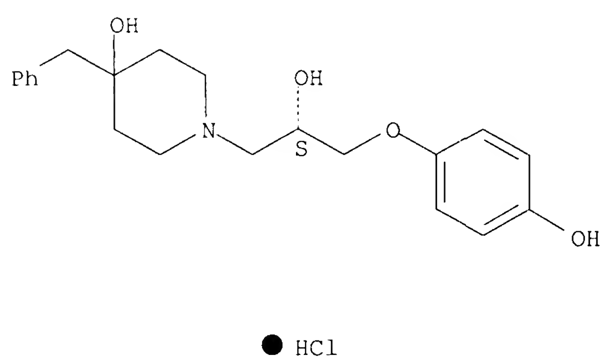
RN 222421-34-3 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[(4-hydroxyphenoxy)methyl]-4-(phenylmethyl)-, hydrochloride, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

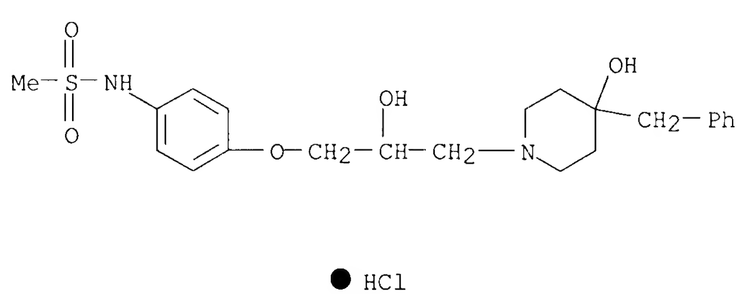


RN 222421-36-5 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[(4-hydroxyphenoxy)methyl]-4-(phenylmethyl)-, hydrochloride, (αS)- (9CI) (CA INDEX NAME)

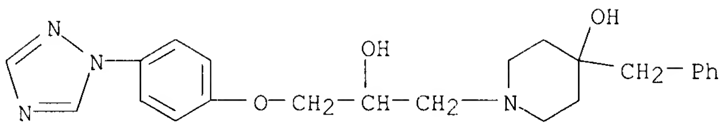
Absolute stereochemistry. Rotation (-).



RN 222421-39-8 CAPLUS
CN Methanesulfonamide, N-[4-[2-hydroxy-3-[4-hydroxy-4-(phenylmethyl)-1-piperidinyl]propoxy]phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



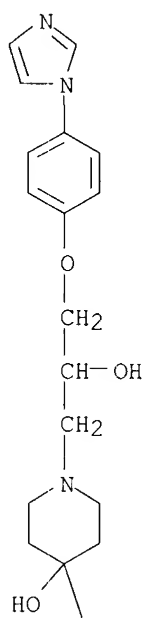
RN 222421-51-4 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-4-(phenylmethyl)-α-[[4-(1H-1,2,4-triazol-1-yl)phenoxy]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)



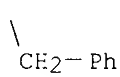
● HCl

RN 222421-53-6 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[[4-(1H-imidazol-1-yl)phenoxy]methyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



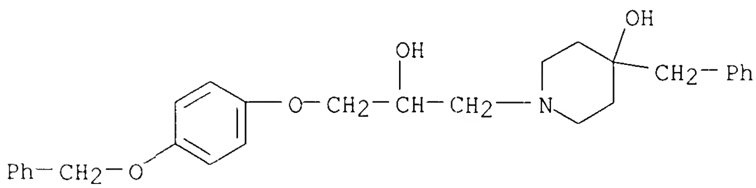
PAGE 2-A



● HCl

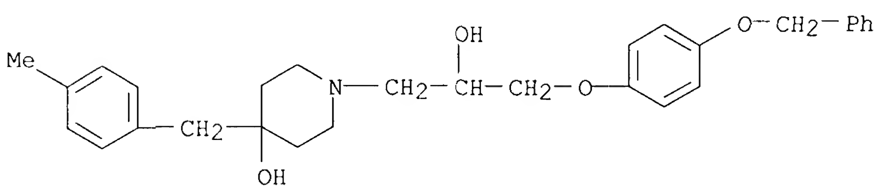
IT 222422-61-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 4-hydroxypiperidines as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers)

RN 222422-61-9 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[[4-(phenylmethoxy)phenoxy]methyl]-4-(phenylmethyl)- (CA INDEX NAME)

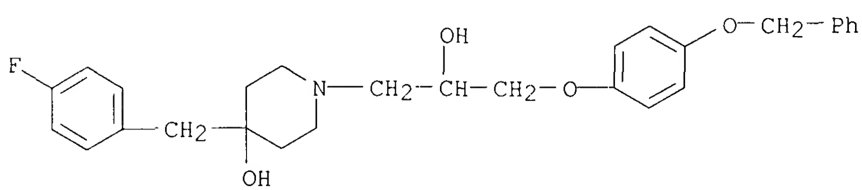


IT 222422-07-3P 222422-09-5P 222422-11-9P
222422-12-0P 222422-13-1P 222422-47-1P
222422-48-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-hydroxypiperidines as NMDA(N-methyl-D-aspartate)-receptor subtype selective blockers)

RN 222422-07-3 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-4-[(4-methylphenyl)methyl]-α-[[4-(phenylmethoxy)phenoxy]methyl]- (CA INDEX NAME)

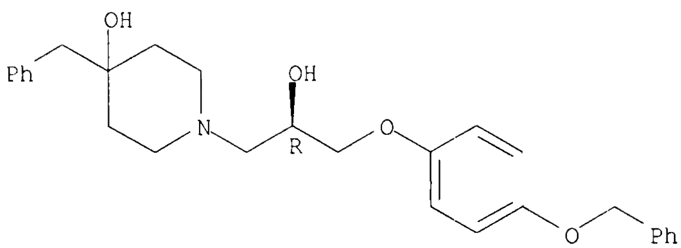


RN 222422-09-5 CAPLUS
CN 1-Piperidineethanol, 4-[(4-fluorophenyl)methyl]-4-hydroxy-α-[[4-(phenylmethoxy)phenoxy]methyl]- (CA INDEX NAME)



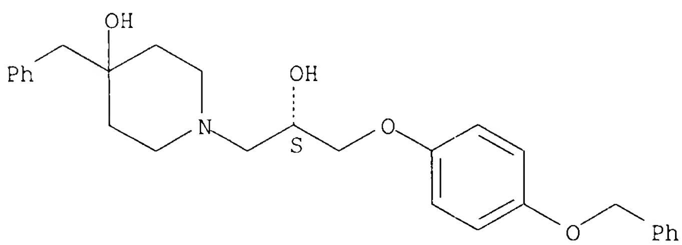
RN 222422-11-9 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[[4-(phenylmethoxy)phenoxy]methyl]-4-(phenylmethyl)-, (αR)- (CA INDEX NAME)

Absolute stereochemistry.

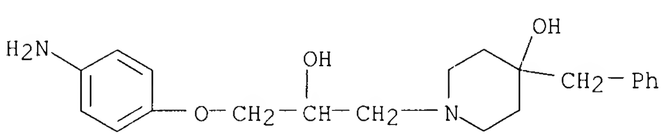


RN 222422-12-0 CAPLUS
CN 1-Piperidineethanol, 4-hydroxy-α-[[4-(phenylmethoxy)phenoxy]methyl]-
4-(phenylmethyl)-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.

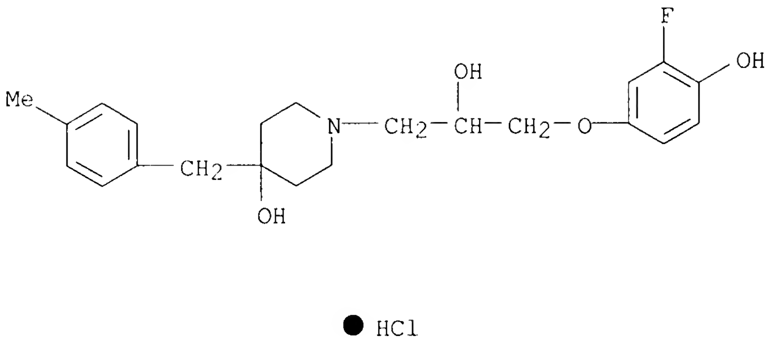


RN 222422-13-1 CAPLUS
CN 1-Piperidineethanol, α-[(4-aminophenoxy)methyl]-4-hydroxy-4-
(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

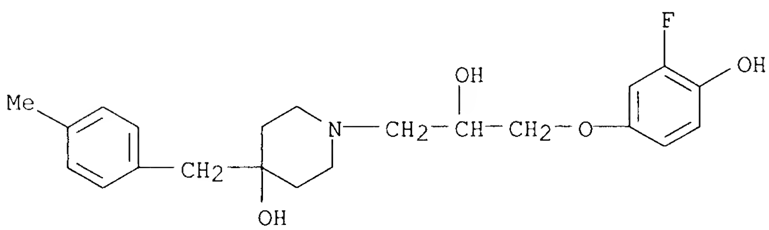


● HCl

RN 222422-47-1 CAPLUS
CN 1-Piperidineethanol, α-[(3-fluoro-4-hydroxyphenoxy)methyl]-4-hydroxy-
4-[(4-methylphenyl)methyl]-, hydrochloride (9CI) (CA INDEX NAME)



RN 222422-48-2 CAPLUS
CN 1-Piperidineethanol, α-[(3-fluoro-4-hydroxyphenoxy)methyl]-4-hydroxy-4-[(4-methylphenyl)methyl]- (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

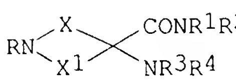
L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1985:149116 CAPLUS
DOCUMENT NUMBER: 102:149116
ORIGINAL REFERENCE NO.: 102:23425a,23428a
TITLE: N-Aryl-α-aminocarboxamides
INVENTOR(S): Van Daele, Georges Henri Paul; De Bruyn, Marcel Frans Leopold; Verdonck, Marc Gustaaf Celine
PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belg.
SOURCE: Eur. Pat. Appl., 95 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

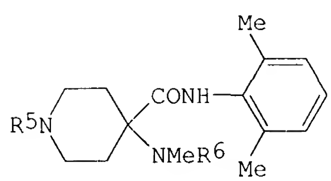
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 121972	A2	19841017	EP 1984-200372	19840314
EP 121972	A3	19870624		
EP 121972	B1	19890524		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
DK 8401396	A	19841012	DK 1984-1396	19840229
AT 43336	T	19890615	AT 1984-200372	19840314
CA 1217484	A1	19870203	CA 1984-449668	19840315
IL 71475	A	19871231	IL 1984-71475	19840409
FI 8401405	A	19841012	FI 1984-1405	19840410
NO 8401422	A	19841012	NO 1984-1422	19840410

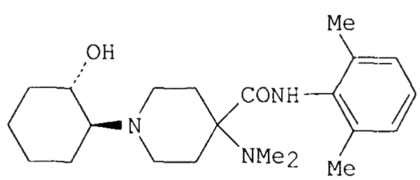
AU 8426706	A	19841018	AU 1984-26706		19840410
AU 562186	B2	19870604			
JP 59225161	A	19841218	JP 1984-70175		19840410
HU 34004	A2	19850128	HU 1984-1388		19840410
HU 193566	B	19871028			
ZA 8402658	A	19851127	ZA 1984-2658		19840410
SU 1313344	A3	19870523	SU 1984-3722251		19840410
PRIORITY APPLN. INFO.:			US 1983-484021	A	19830411
			US 1984-581948	A	19840221
			EP 1984-200372	A	19840314

OTHER SOURCE(S): MARPAT 102:149116

GI


I


II


III

AB Antiarrhythmic title compds. I [X, X1 = (un)substituted (CH2)n; n = 1-3; x + x1 = 3 or 4 CH2 groups; R = H, (un)substituted alkenyl, N-containing heterocycle, cycloalkyl, acyl, etc; R1, R3, R4 = H, alkyl, acyl; R1R3 = CH2; NR3R4 = piperidino, pyrrolidino, morpholino; R2 = aryl] (>250 compds.) were prepared Thus piperidinecarboxylate II (R5 = CO2CH2Ph, R6 = H) was methylated to II (R5 = CO2CH2Ph, R6 = Me), which was treated with H to give II (R5 = H, R6 = Me). II (R5 = H, R6 = Me) reacted with cyclohexene oxide to give trans-(hydroxycyclohexyl)piperidinecarboxamide III. III had a lowest ED of 0.04 mg/kg i.v. in dogs against multifocal ventricular arrhythmia, induced by ligation of the coronary artery. This effect lasted 240 min.

IT 95608-26-7P

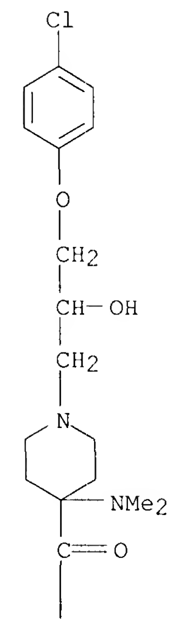
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation and antiarrhythmic activity of)

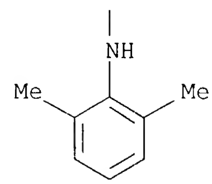
RN 95608-26-7 CAPLUS

CN 4-Piperidinecarboxamide, 1-[3-(4-chlorophenoxy)-2-hydroxypropyl]-4-(dimethylamino)-N-(2,6-dimethylphenyl)- (CA INDEX NAME)

PAGE 1-A



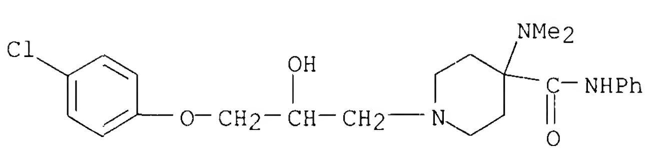
PAGE 2-A



IT 95608-19-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 95608-19-8 CAPLUS
CN 4-Piperidinecarboxamide, 1-[3-(4-chlorophenoxy)-2-hydroxypropyl]-4-(dimethylamino)-N-phenyl-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

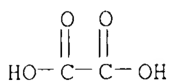
CM 1

CRN 95608-18-7
CMF C23 H30 Cl N3 O3



CM 2

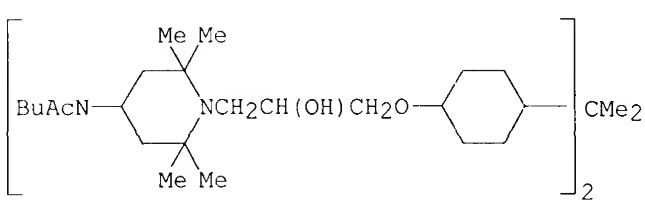
CRN 144-62-7
CMF C2 H2 O4



L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1979:6902 CAPLUS
DOCUMENT NUMBER: 90:6902
ORIGINAL REFERENCE NO.: 90:1259a,1262a
TITLE: Piperidine derivatives useful as polymer stabilizers
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Neth. Appl., 177 pp.
CODEN: NAXXAN
DOCUMENT TYPE: Patent
LANGUAGE: Dutch
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
NL 7800505	A	19780718	NL 1978-505		19780116
JP 53101380	A	19780904	JP 1977-3285		19770114
JP 62042898	B	19870910			
FR 2377381	A1	19780811	FR 1978-999		19780113
FR 2377381	B1	19820108			
BE 862958	A1	19780717	BE 1978-184368		19780116
GB 1574999	A	19800917	GB 1978-1715		19780116
US 4371644	A	19830201	US 1980-168271		19800710
PRIORITY APPLN. INFO.:			JP 1977-3285	A	19770114
			US 1978-866957	A3	19780105

GI


I

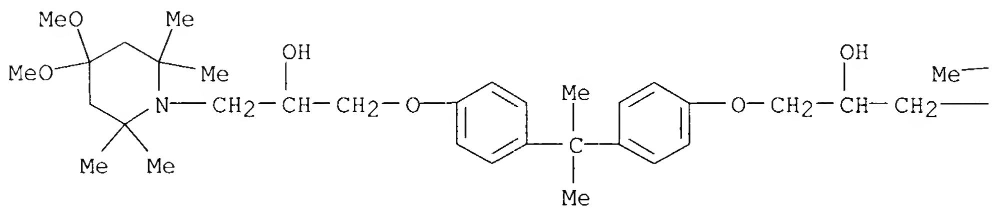
AB Compds. containing 2 or 3 substituted or unsubstituted 2,2,6,6-tetramethylpiperidinyl groups attached to a central radical by groups containing ether moieties and preferably OH groups are useful as polymer stabilizers and have improved evaporation, extraction, and heat resistance. Thus, a mixture of 5.1 g 4-(N-butylacetamido)-2,2,6,6-tetramethylpiperidine [67778-07-8] and 3.5 g 2,2-bis[4-(2,3-epoxypropoxy)cyclohexyl]propane [13410-58-7] was heated 5 h at 200-10°, giving 2,2-bis[4-[3-[4-(N-

butylacetamido)-2,2,6,6-tetramethylpiperidino]-2-
hydroxypropoxy]cyclohexyl]propane (I) [67812-46-8]. A mixture of polypropylene [9003-07-0] 100, stearyl 2-(4-hydroxy-3,5-di-tert-butylphenyl)propionate 0.2, and I 0.25 part was processed into a 0.1 mm sheet by standard methods and exposed to light in an accelerated testing apparatus

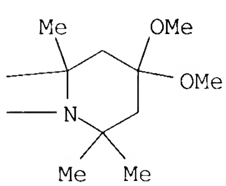
This composition had time to 50% loss of elongation 6.6 times that of a control without I, compared to 2.0 times for a com. stabilizer, Tinuvin 327.

IT 67777-89-3
RL: USES (Uses)
(light stabilizers, for plastics)
RN 67777-89-3 CAPLUS
CN 1-Piperidineethanol, α,α'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis[4,4-dimethoxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1978:580832 CAPLUS
DOCUMENT NUMBER:	89:180832
ORIGINAL REFERENCE NO.:	89:28101a,28104a
TITLE:	Piperidine derivatives useful as stabilizers for polymers
INVENTOR(S):	Soma, Nobuo; Morimura, Syoji; Yoshioka, Takao; Kurumada, Tomoyuki
PATENT ASSIGNEE(S):	Sankyo Co., Ltd., Japan
SOURCE:	Ger. Offen., 192 pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	2

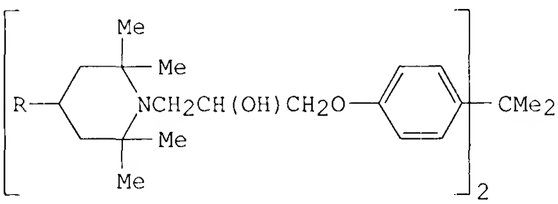
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2801470	A1	19780727	DE 1978-2801470	19780113
JP 53101380	A	19780904	JP 1977-3285	19770114

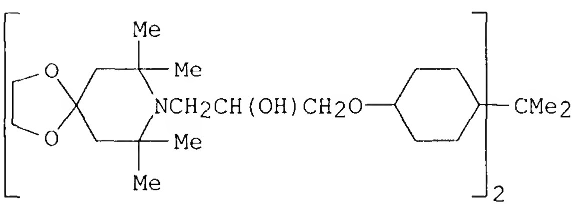
JP 62042898	B	19870910			
FR 2377381	A1	19780811	FR 1978-999		19780113
FR 2377381	B1	19820108			
BE 862958	A1	19780717	BE 1978-184368		19780116
GB 1574999	A	19800917	GB 1978-1715		19780116
US 4371644	A	19830201	US 1980-168271		19800710
PRIORITY APPLN. INFO.:			JP 1977-3285	A	19770114
			US 1978-866957	A3	19780105

OTHER SOURCE(S): MARPAT 89:180832

GI



I



II

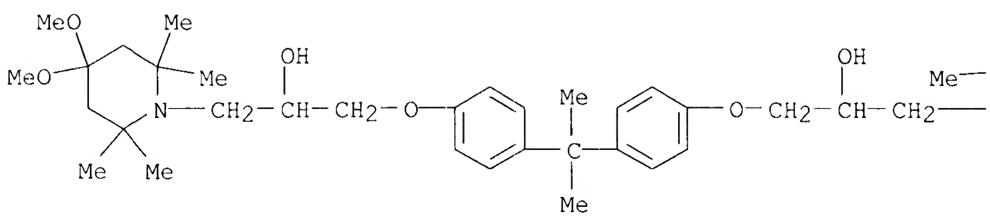
AB 2,2-Bis[4-[2-hydroxy-3-(2,2,6,6-tetramethylpiperidino)propoxy]phenyl]propane (I, R = H) [67777-70-2], I (R = OH) [67778-13-6], I [R = 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionyloxy] [67778-14-7], tris[2-hydroxy-3-(2,2,6,6-tetramethylpiperidino)propyl] isocyanurate [67901-20-6], bis[2-hydroxy-3-(4-hydroxy-2,2,6,6-tetramethylpiperidino)propyl] 1,2-cyclohexanedicarboxylate [67777-81-5], bis[3-(4-benzoyloxy-2,2,6,6-tetramethylpiperidino)-2-hydroxypropyl] sebacate [67777-79-1], 1,3-bis[3-(4-benzoyloxy-2,2,6,6-tetramethylpiperidino)-2-hydroxypropoxy]-2-hydroxypropane [67777-84-8], 2,2-bis[4-[2-hydroxy-3-(7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl)propoxy]cyclohexyl]propane (II) [67777-93-9], 2,2-bis[4-[2-hydroxy-3-(7,7,9,9-tetramethyl-3-octyl-2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl)propoxy]cyclohexyl]propane [67778-00-1], and 38 similar compds. are prepared for use as stabilizers for plastics. The stabilizers are resistant to volatilization and extraction from plastics. Thus, 2,2,6,6-tetramethylpiperidine [768-66-1] and 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane [1675-54-3] were used to prepare I (R = H). The addition of 0.25% I (R = H) and 0.2% phenolic antioxidant to polypropylene [9003-07-0] increased the UV light resistance by a factor of 4.7.

IT 67777-89-3
RL: USES (Uses)
(stabilizers, for plastics)

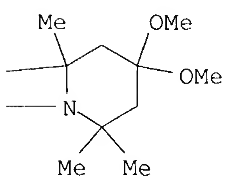
RN 67777-89-3 CAPLUS

CN 1-Piperidineethanol, α,α'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis[4,4-dimethoxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



=> d his

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FILE 'REGISTRY' ENTERED AT 14:39:16 ON 10 MAR 2008

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L2            2 S L1
L3           37 S L1 FULL
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FILE 'CAPLUS' ENTERED AT 14:39:45 ON 10 MAR 2008

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L4            7 S L3
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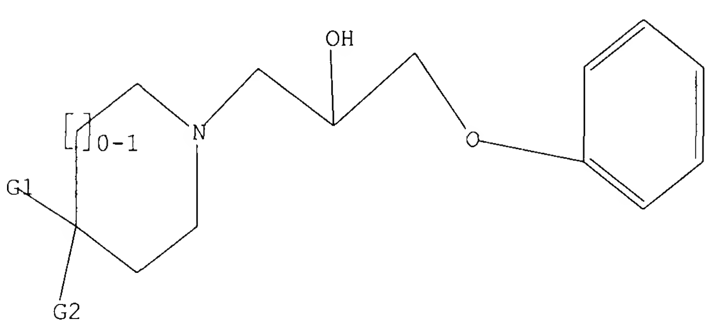
L1 HAS NO ANSWERS

L1 STR



G1 C,O

G2 C,O,N

Structure attributes must be viewed using STN Express query preparation.

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L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:41477 CAPLUS
DOCUMENT NUMBER: 140:93937
TITLE: Preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors
INVENTOR(S): Hossain, Nafizal; Ivanova, Svetlana; Mensonides-Harsema, Marguerite
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 281 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005295	A1	20040115	WO 2003-SE1185	20030707
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2492122	A1	20040115	CA 2003-2492122	20030707
AU 2003243122	A1	20040123	AU 2003-243122	20030707
EP 1521757	A1	20050413	EP 2003-762957	20030707
EP 1521757	B1	20080130		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003012560	A	20050510	BR 2003-12560	20030707
CN 1675218	A	20050928	CN 2003-819146	20030707
JP 2005537255	T	20051208	JP 2004-519472	20030707
NZ 537259	A	20060831	NZ 2003-537259	20030707
CN 1974574	A	20070606	CN 2006-10143556	20030707
AT 385235	T	20080215	AT 2003-762957	20030707
IN 2004DN04014	A	20070427	IN 2004-DN4014	20041216
ZA 2005000024	A	20060222	ZA 2005-24	20050103
MX 2005PA00278	A	20050331	MX 2005-PA278	20050104
US 2005245741	A1	20051103	US 2005-520699	20050107
NO 2005000635	A	20050331	NO 2005-635	20050204
PRIORITY APPLN. INFO.:			SE 2002-2133 A	20020708
			CN 2003-819146 A3	20030707
			WO 2003-SE1185 W	20030707

OTHER SOURCE(S): MARPAT 140:93937

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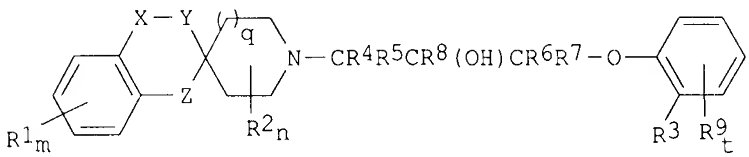
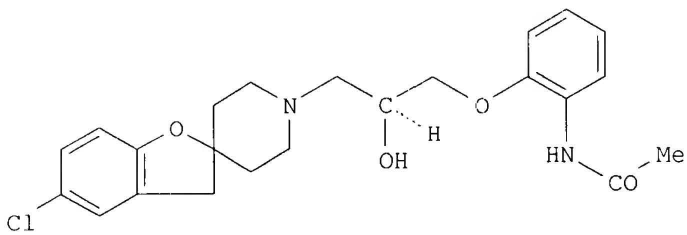


I



II

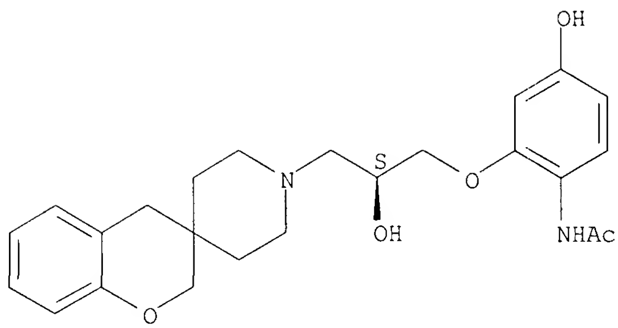
AB The invention provides tricyclic spiropiperidines or spiropyrrolidines (shown as I; variables defined below; e.g. II), processes for their preparation, pharmaceutical compns. containing them and their use in therapy for disorders affected by modulation of chemokine receptors (no data). For I: m is 0-4; each R1 = halogen, cyano, hydroxy, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy or sulfonamido; either X = a bond, -CH2-, -O- or -C(O)- and Y = a bond, -CH2-, -O- or -C(O)-, or X and Y together = -CH:CMe- or -CMe:CH-, and Z = a bond, -O-, -NH- or -CH2-, provided that only one of X, Y and Z can be a bond at any one time and provided that X and Y do not both simultaneously = -O- or -C(O)-. N = 0-2; each R2 = halogen or C1-C6 alkyl; q = 0-1; R3 = -NHC(O)R10, -C(O)NR11R12 or -COOR12a; R4, R5, R6, R7 and R8 = H or a C1-C6 alkyl group; t = 0-2; each R9 = halogen, cyano, hydroxy, carboxy, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 haloalkyl, or C1-C6 alkyl; addnl. details are given in the claims. Methods of preparation are claimed and >200 example prepns. are included. For example, II was prepared in 2 steps starting from N-(2-hydroxyphenyl)acetamide, ((2S)-oxiran-2-yl)methyl and Cs2CO3 in DMF to give N-[2-[((2S)-oxiran-2-yl)methoxy]phenyl]acetamide as an intermediate, which was reacted with 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] in EtOH to give II.

IT 644969-17-5P 644969-18-6P 644969-79-9P
644969-81-3P 644969-83-5P 644969-85-7P
644969-87-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biolcgical study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

RN 644969-17-5 CAPLUS

CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[2H-1-benzopyran-3(4H),4'-piperidin]-1'-ylpropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

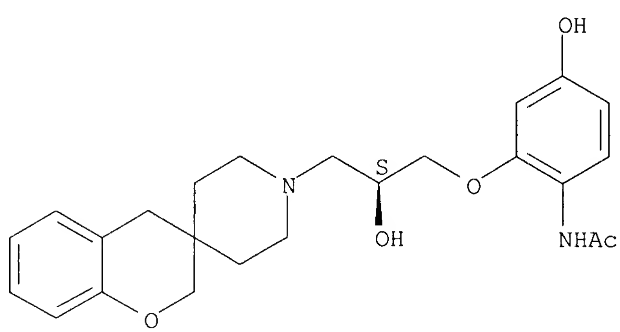


RN 644969-18-6 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[2H-1-benzopyran-3(4H),4'-piperidin]-1'-ylpropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

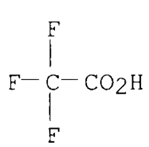
CRN 644969-17-5
CMF C24 H30 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

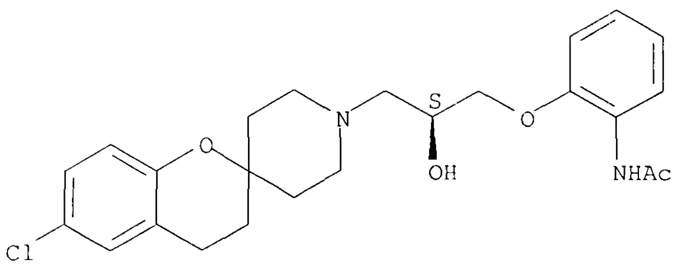


RN 644969-79-9 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(6-chloro-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

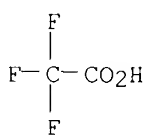
CRN 644969-78-8
CMF C24 H29 Cl N2 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

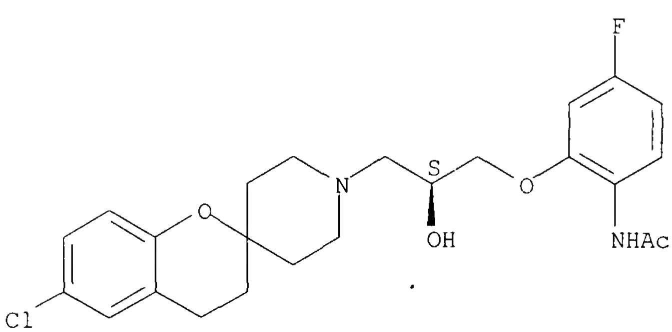


RN 644969-81-3 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(6-chloro-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluorophenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

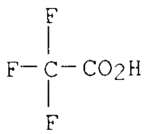
CRN 644969-80-2
CMF C24 H28 Cl F N2 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

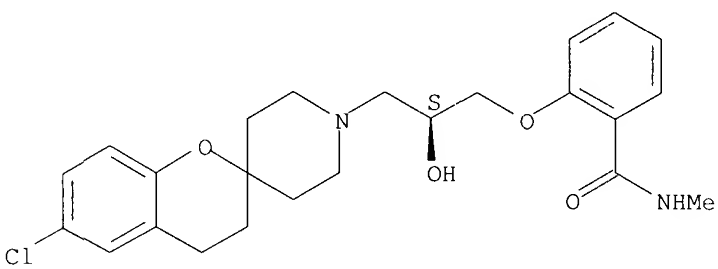


RN 644969-83-5 CAPLUS
CN Benzamide, 2-[(2S)-3-(6-chloro-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-methyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

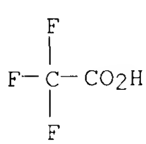
CRN 644969-82-4
CMF C24 H29 Cl N2 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

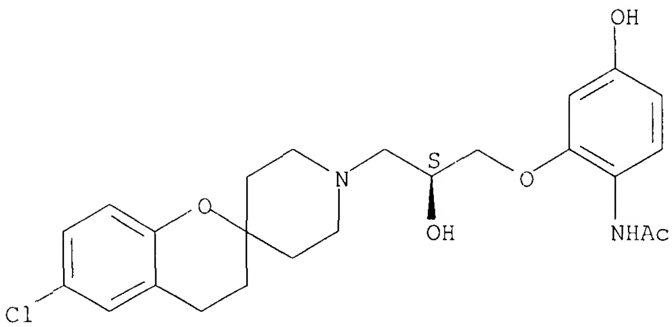


RN 644969-85-7 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(6-chloro-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

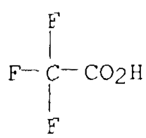
CRN 644969-84-6
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

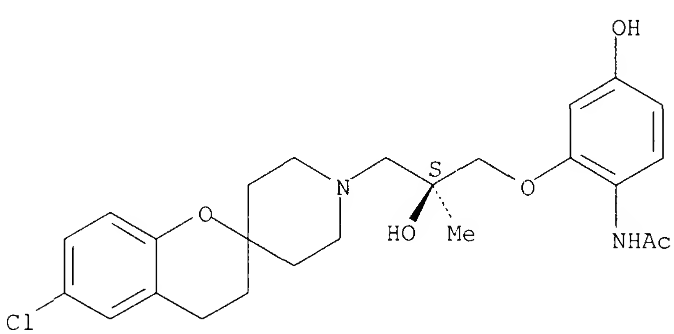


RN 644969-87-9 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(6-chloro-3,4-dihydrospiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

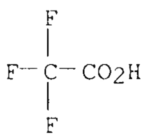
CRN 644969-86-8
CMF C25 H31 Cl N2 O5

Absolute stereochemistry.



CM 2

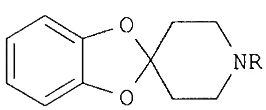
CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

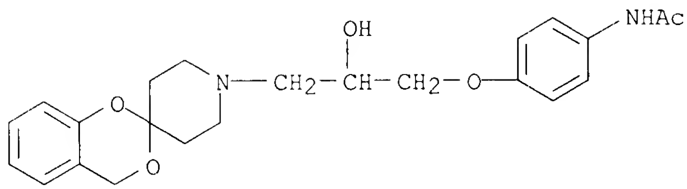
L4 ANSWER 2 OF 2 CAPLUS

ACCESSION NUMBER: 1996:736623 CAPLUS
DOCUMENT NUMBER: 126:89321
TITLE: Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines]
AUTHOR(S): Pujol, M. D.; Rosell, G.; Guillaumet, G.
CORPORATE SOURCE: Fac. Farm., Univ. Barcelona, Barcelona, 08028, Spain
SOURCE: European Journal of Medicinal Chemistry (1996), 31(11), 889-894
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of a new series of spiropiperidines is reported. Some of these compds. showed interesting adrenergic activity. The biol. activities of the new compds. were evaluated on guinea pig atria (β1), guinea-pig trachea (β2), and rat vas deferens (α). Three of the compds., e.g. I [R = CH2CH(OH)CH2OC6H4NHCOMe-4], showed activity comparable to propranolol, in spite of being tertiary amines.
IT 185316-94-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines])
RN 185316-94-3 CAPLUS
CN Acetamide, N-[4-(2-hydroxy-3-spiro[4H-1,3-benzodioxin-2,4'-piperidin]-1'-ylpropoxy)phenyl]- (9CI) (CA INDEX NAME)



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FILE 'REGISTRY' ENTERED AT 16:02:58 ON 10 MAR 2008

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L1              STRUCTURE UPLOADED
L2            1 S L1
L3           13 S L1 FULL
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FILE 'CAPLUS' ENTERED AT 16:03:45 ON 10 MAR 2008

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L4            2 S L3
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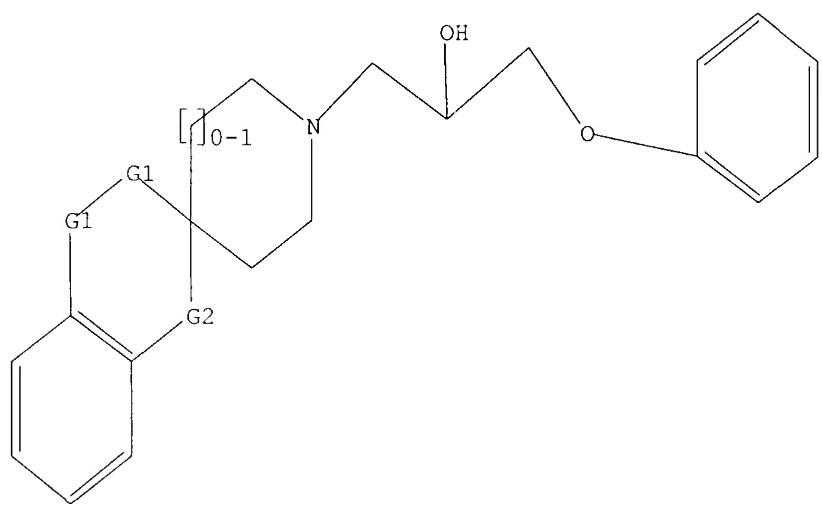
L1 HAS NO ANSWERS
L1 STR



G1 C,O
G2 C,O,N

Structure attributes must be viewed using STN Express query preparation.

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L8 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:90972 CAPLUS

10/579,545

DOCUMENT NUMBER: 148:191862
TITLE: Preparation of spirobenzofuranpiperidines as modulators of chemokine CCR1 receptor activity
INVENTOR(S): Elkins, Barry; Ennis, David; Eriksson, Tomas; Gibson, Scott; Gu, Eric; Hassall, Ian; Hemmerling, Martin; Josefsson, Bo-Goeran; Ivanova, Svetlana; Kavitake, Santosh; Kumar, Sythana Suresh; Kumar, Vinod; Lingesha, Sidda; Mensonides-Harsema, Marguerite; Merifield, Eric; Mo, John; Pavey, John; Pimm, Austen; Reuberson, James; Rogers, Mike; Schulz, Haakan; Strandberg, Per; Zhengyu, Wang
PATENT ASSIGNEE(S): AstraZeneca AB, Swed.
SOURCE: PCT Int. Appl., 135pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

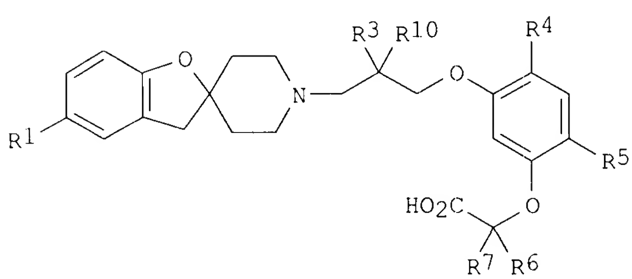
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008010765	A1	20080124	WO 2007-SE694	20070717

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-831776P P 20060719

GI



I

AB Title compds. [I; R1 = halo; R3 = H, OH; R10 = H, alkyl; R4 = CONR8R9, NHCOR11, NHCONR8R9; R8, R9 = H, alkyl, cycloalkyl; NR8R9 = 4-7 membered (hydroxy-substituted) heterocyclyl; R11 = (substituted) alkyl, alkenyl, cycloalkyl, adamantyl, cycloalkenyl, Ph, heterocyclyl; R5 = H, halo; R6, R7 = H, alkyl; CR6R7 = atoms to form 3-7 membered cycloalkyl], were prepared Thus, title compound 2-[2-chloro-5-[[(2S)-3-[5-chloro-3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]-2-hydroxypropyl]oxy]-4-[(methylamino)carbonyl]phenoxy]-2-methylpropanoic acid was prepared in 10 steps from 1-Boc-4-piperidinone, trimethylsulfoxonium iodide,

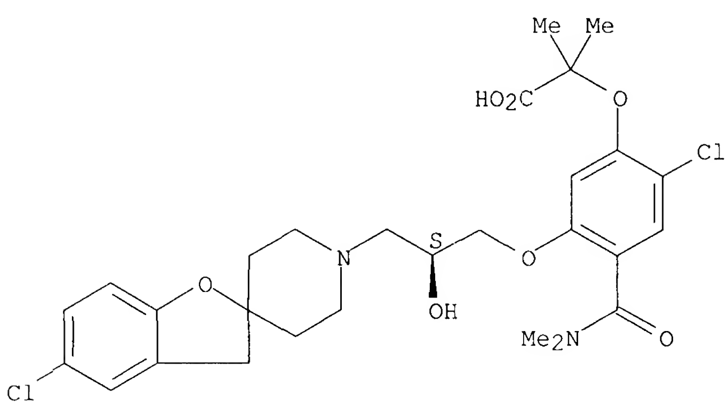
2-bromo-4-chloroanisole, Me 2-hydroxy-4-methoxybenzoate, methylamine, 3-nitrobenzenesulfonic acid (S)-1-oxiranylmethyl ester, and Et 2-bromoisobutyrate. In human CCR1 receptor binding assays, I showed affinity at <20 μM.

IT 1003567-03-0P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of spirobenzofuranpiperidines as modulators of
chemokine CCR1 receptor activity)

RN 1003567-03-0 CAPLUS

CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.



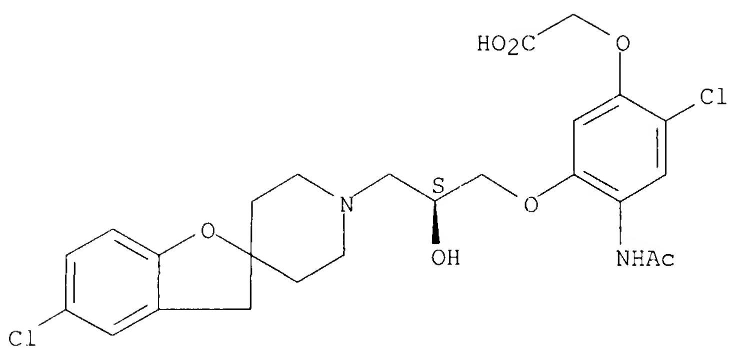
● HCl

IT 1003566-89-9P 1003566-90-2P 1003566-91-3P
1003566-92-4P 1003566-93-5P 1003566-95-7P
1003566-96-8P 1003566-97-9P 1003566-98-0P
1003566-99-1P 1003567-00-7P 1003567-01-8P
1003567-02-9P 1003567-04-1P 1003567-05-2P
1003567-06-3P 1003567-07-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of spirobenzofuranpiperidines as modulators of
chemokine CCR1 receptor activity)

RN 1003566-89-9 CAPLUS

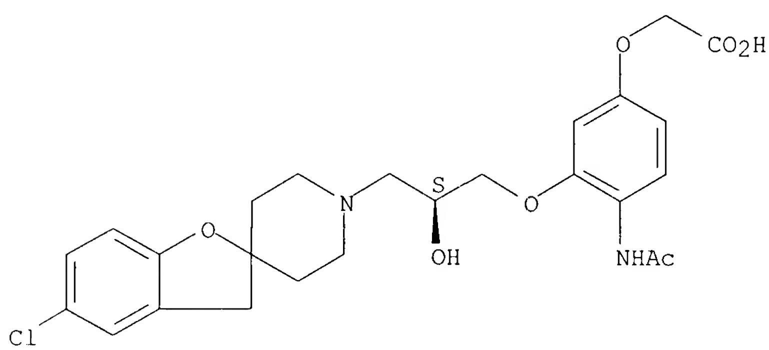
CN Acetic acid, 2-[4-(acetylamino)-2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



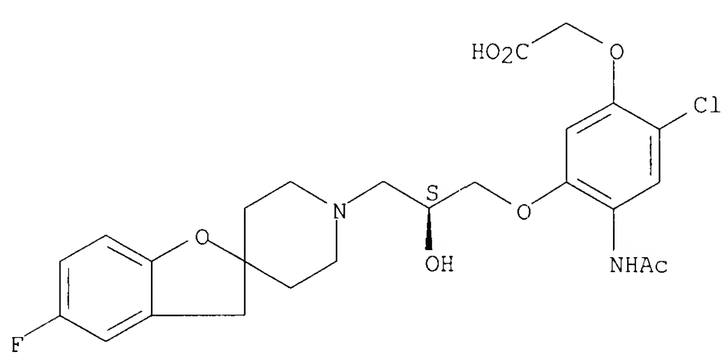
RN 1003566-90-2 CAPLUS
CN Acetic acid, 2-[4-(acetylamino)-3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 1003566-91-3 CAPLUS
CN Acetic acid, 2-[4-(acetylamino)-2-chloro-5-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]- (CA INDEX NAME)

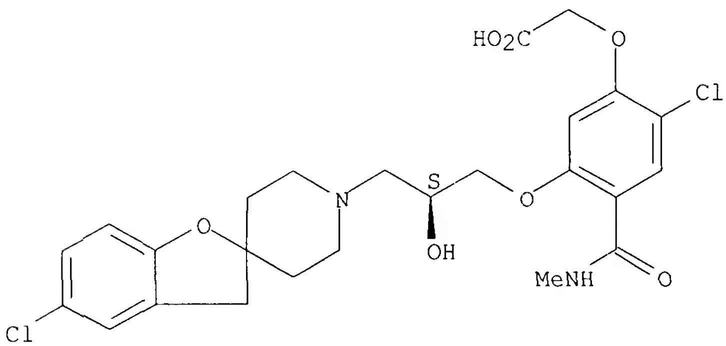
Absolute stereochemistry.



RN 1003566-92-4 CAPLUS

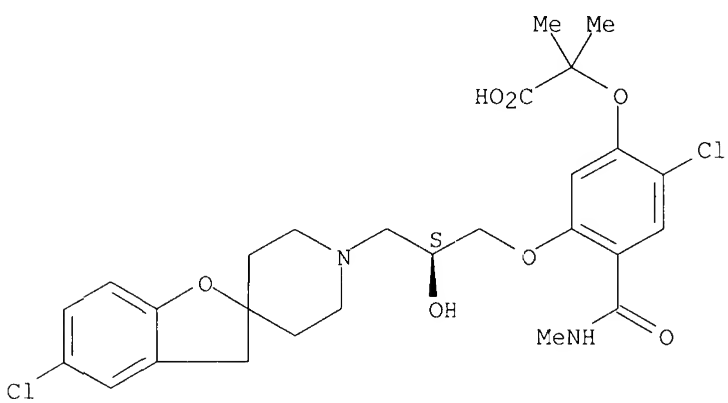
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



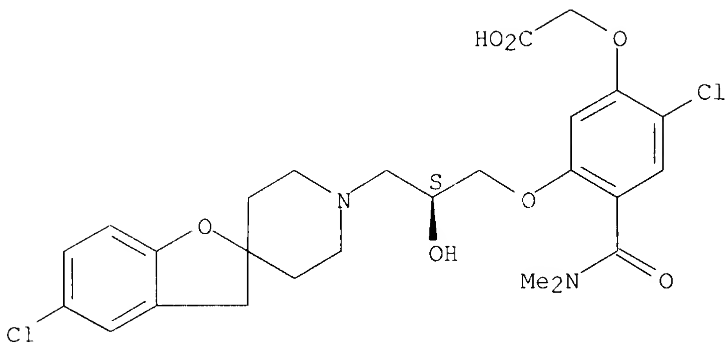
RN 1003566-93-5 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl- (CA INDEX NAME)

Absolute stereochemistry.



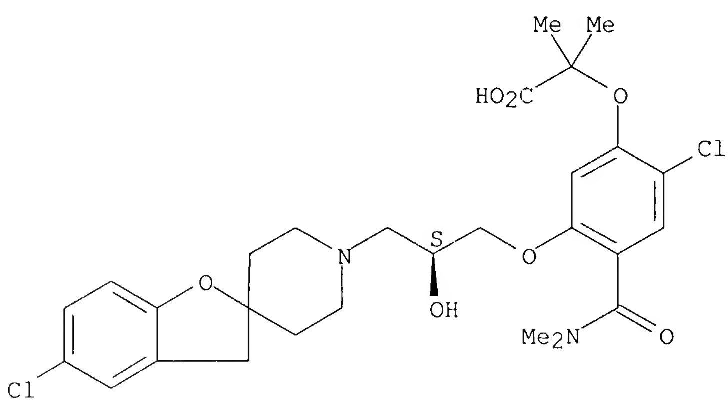
RN 1003566-95-7 CAPLUS
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



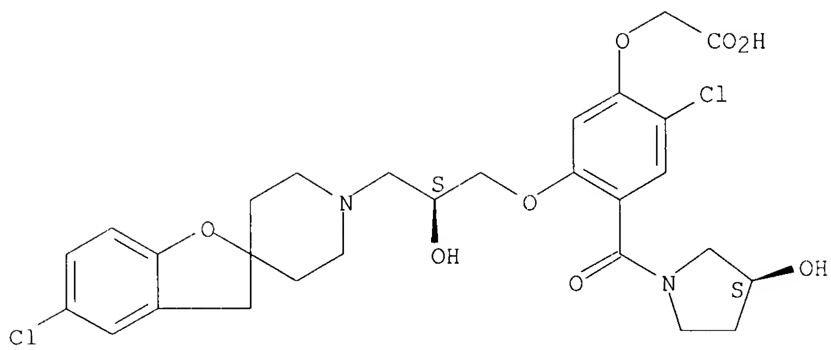
RN 1003566-96-8 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl- (CA INDEX NAME)

Absolute stereochemistry.



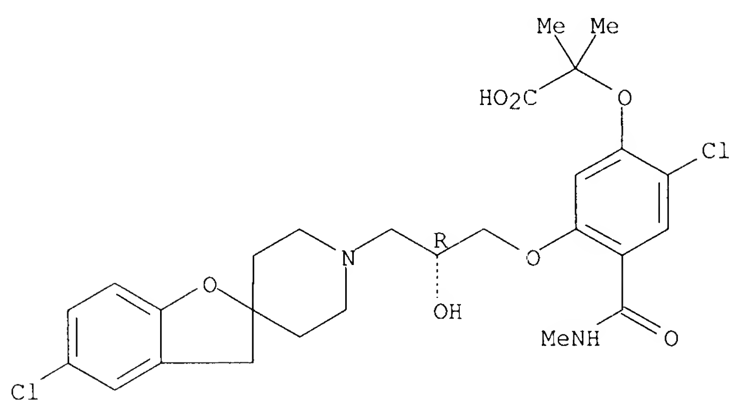
RN 1003566-97-9 CAPLUS
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[[(3S)-3-hydroxy-1-pyrrolidinyl]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.

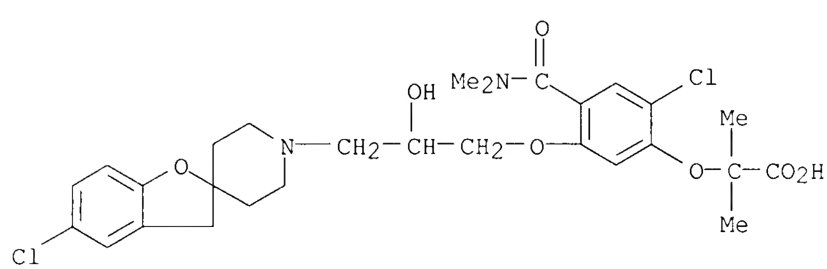


RN 1003566-98-0 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2R)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl- (CA INDEX NAME)

Absolute stereochemistry.



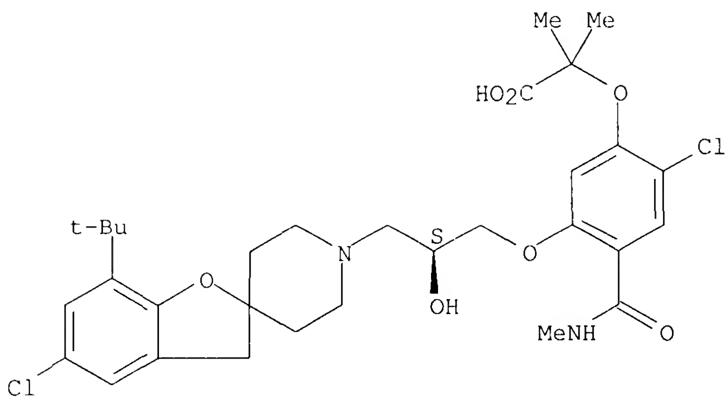
RN 1003566-99-1 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl- (CA INDEX NAME)



RN 1003567-00-7 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-[5-chloro-7-(1,1-dimethylethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]-2-

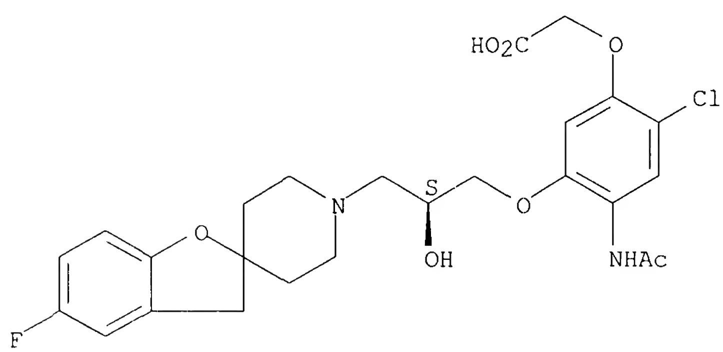
hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl- (CA INDEX NAME)

Absolute stereochemistry.



RN 1003567-01-8 CAPLUS
CN Acetic acid, 2-[4-(acetylamino)-2-chloro-5-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]-, hydrochloride (1:1) (CA INDEX NAME)

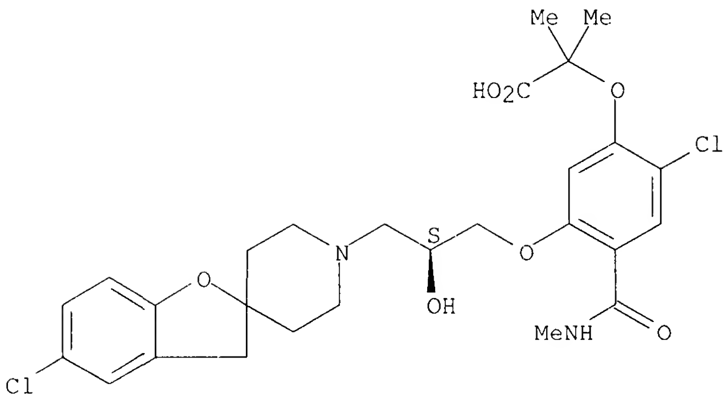
Absolute stereochemistry.



● HCl

RN 1003567-02-9 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, sodium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry.

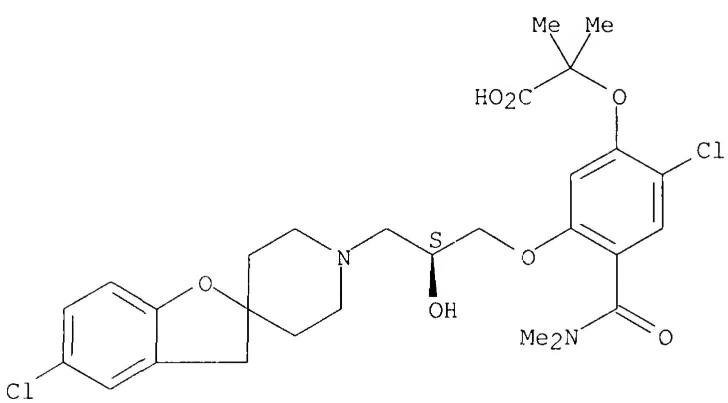


RN 1003567-04-1 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

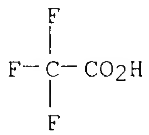
CRN 1003566-96-8
CMF C28 H34 Cl2 N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

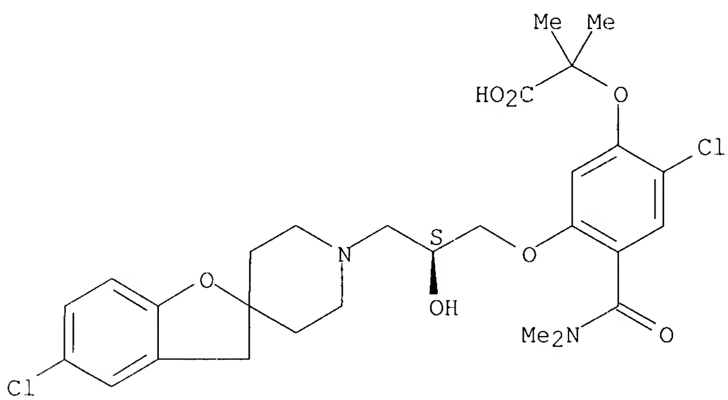


RN 1003567-05-2 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, 4-methylbenzenesulfonate (1:1) (CA INDEX NAME)

CM 1

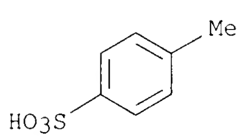
CRN 1003566-96-8
CMF C28 H34 Cl2 N2 O7

Absolute stereochemistry.



CM 2

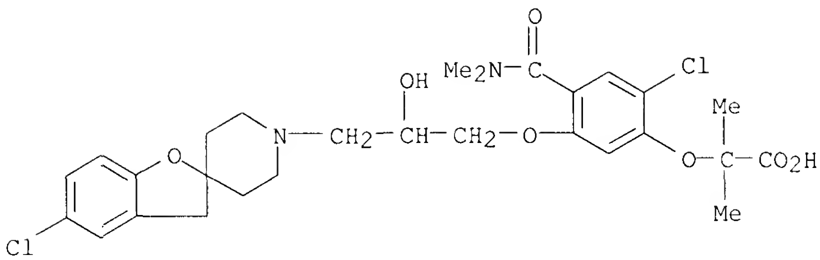
CRN 104-15-4
CMF C7 H8 O3 S



RN 1003567-06-3 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

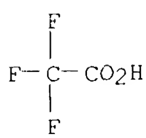
CM 1

CRN 1003566-99-1
CMF C28 H34 Cl2 N2 O7



CM 2

CRN 76-05-1
CMF C2 H F3 O2

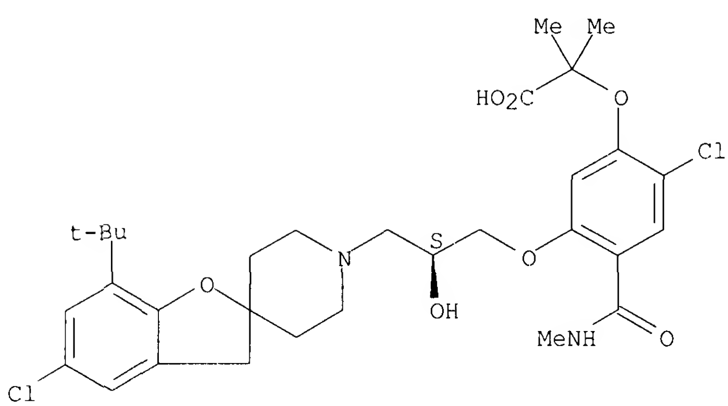


RN 1003567-07-4 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-[5-chloro-7-(1,1-dimethylethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

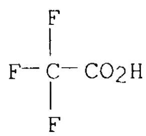
CRN 1003567-00-7
CMF C31 H40 Cl2 N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

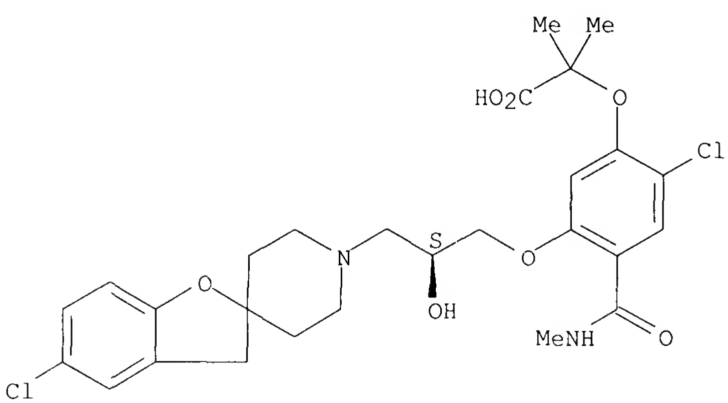


IT 1003567-18-7P 1003567-23-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of spirobenzofuranpiperidines as modulators of chemokine CCR1 receptor activity)
RN 1003567-18-7 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

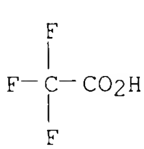
CRN 1003566-93-5
CMF C27 H32 Cl2 N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

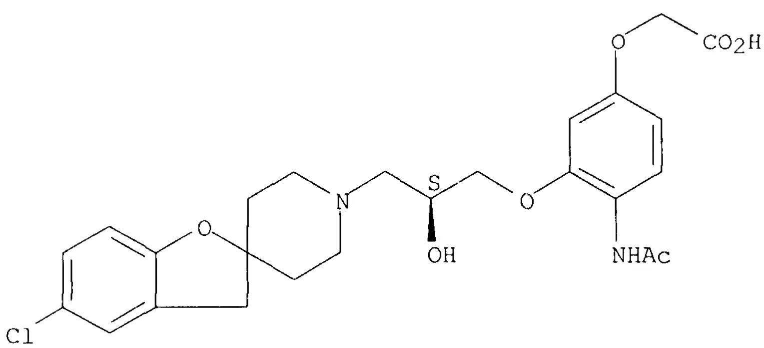


RN 1003567-23-4 CAPLUS
CN Acetic acid, 2-[4-(acetylamino)-3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

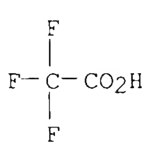
CRN 1003566-90-2
CMF C25 H29 Cl N2 O7

Absolute stereochemistry.



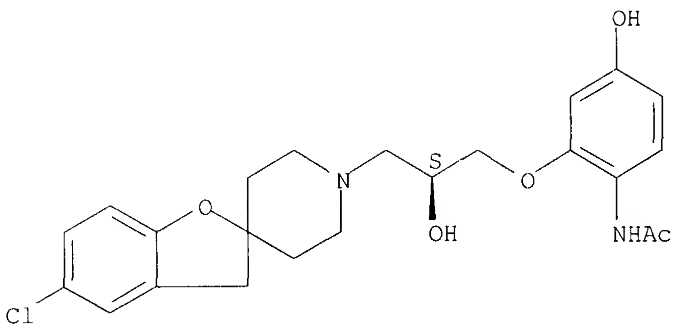
CM 2

CRN 76-05-1
CMF C2 H F3 O2



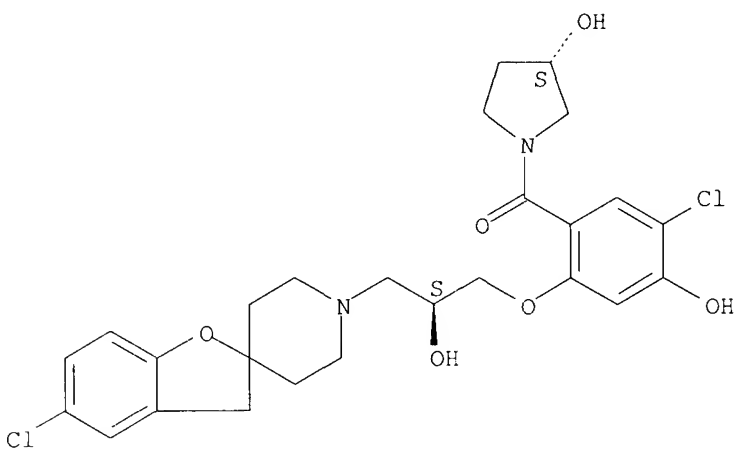
IT 644968-75-2 644971-03-9 1003567-40-5
1003567-41-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of spirobenzofuranpiperidines as modulators of chemokine CCR1 receptor activity)
RN 644968-75-2 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.

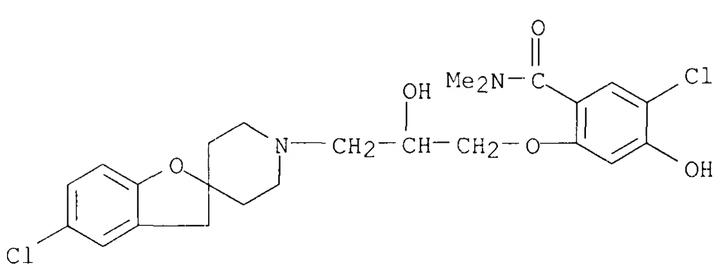


RN 644971-03-9 CAPLUS
CN Methanone, [5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl][(3S)-3-hydroxy-1-pyrrolidinyl]- (CA INDEX NAME)

Absolute stereochemistry.

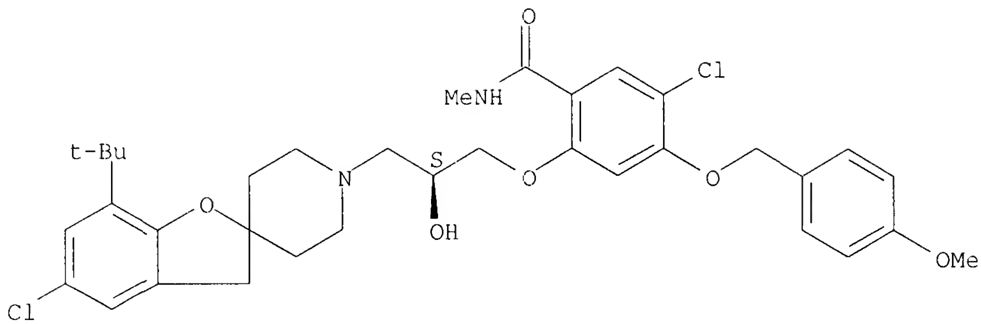


RN 1003567-40-5 CAPLUS
CN Benzamide, 5-chloro-2-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N,N-dimethyl- (CA INDEX NAME)



RN 1003567-41-6 CAPLUS
CN Benzamide, 5-chloro-2-[(2S)-3-[5-chloro-7-(1,1-dimethylethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

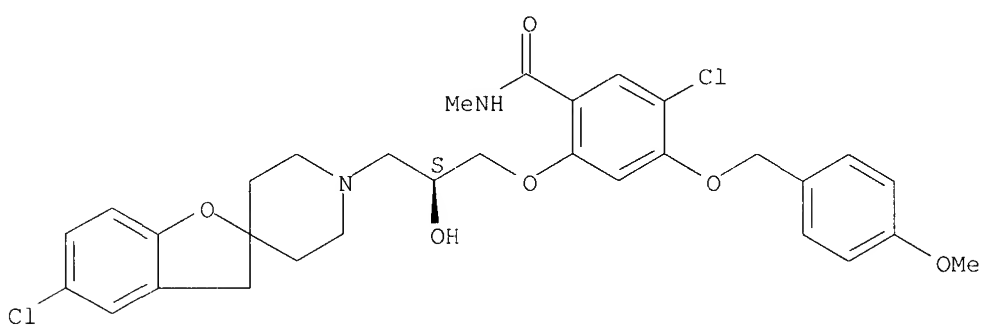


IT 1003567-11-0P 1003567-13-2P 1003567-17-6P
1003567-20-1P 1003567-21-2P 1003567-22-3P
1003567-24-5P 1003567-27-8P 1003567-28-9P
1003567-29-0P 1003567-33-6P 1003567-35-8P
1003567-36-9P 1003567-37-0P 1003567-43-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of spirobenzofuranpiperidines as modulators of chemokine CCR1 receptor activity)

RN 1003567-11-0 CAPLUS

CN Benzamide, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



RN 1003567-13-2 CAPLUS

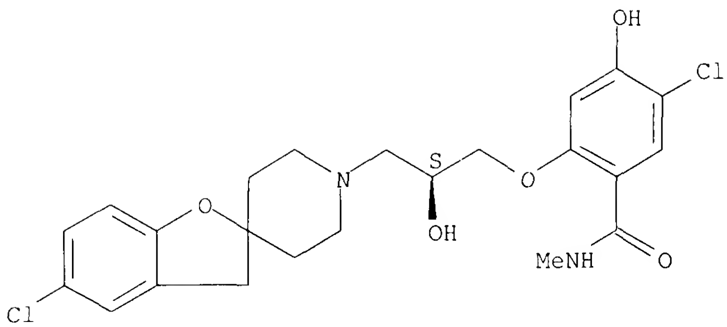
CN Benzamide, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 1003567-12-1

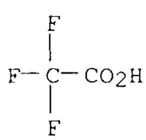
CMF C23 H26 Cl2 N2 O5

Absolute stereochemistry.



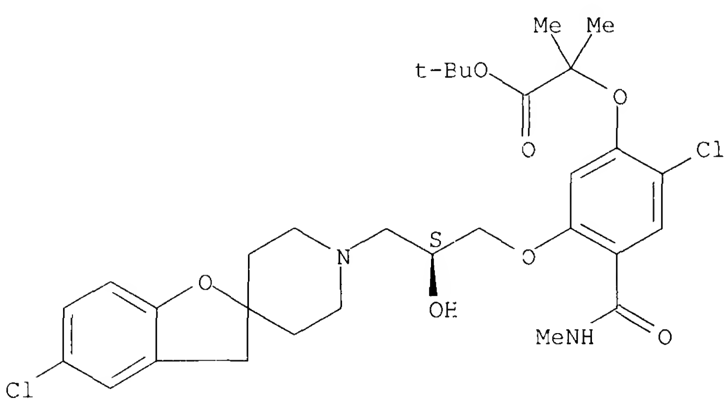
CM 2

CRN 76-05-1
CMF C2 H F3 O2



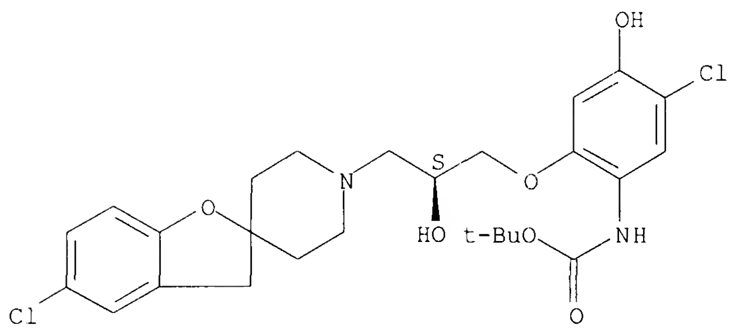
RN 1003567-17-6 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.



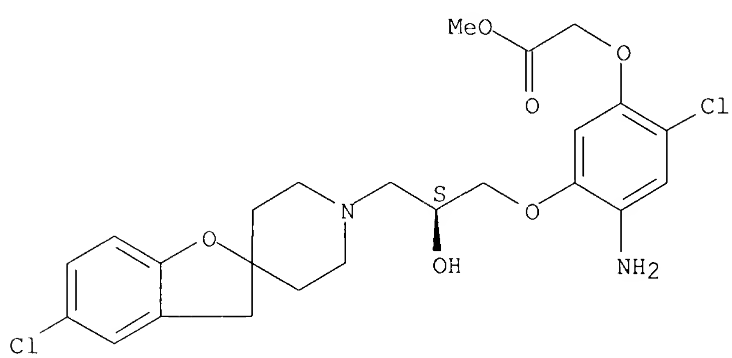
RN 1003567-20-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



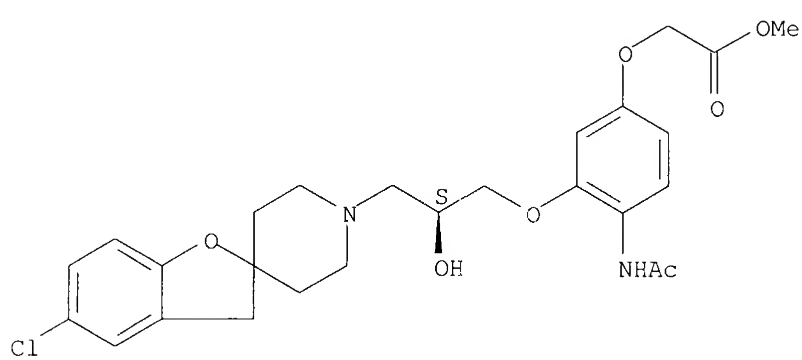
RN 1003567-21-2 CAPLUS
CN Acetic acid, 2-[4-amino-2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 1003567-22-3 CAPLUS
CN Acetic acid, 2-[4-(acetylamino)-3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]-, methyl ester (CA INDEX NAME)

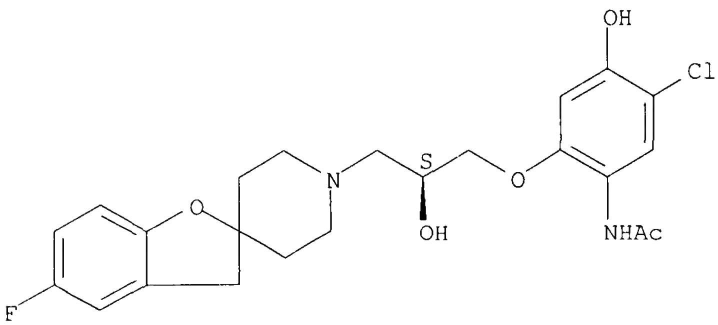
Absolute stereochemistry.



RN 1003567-24-5 CAPLUS

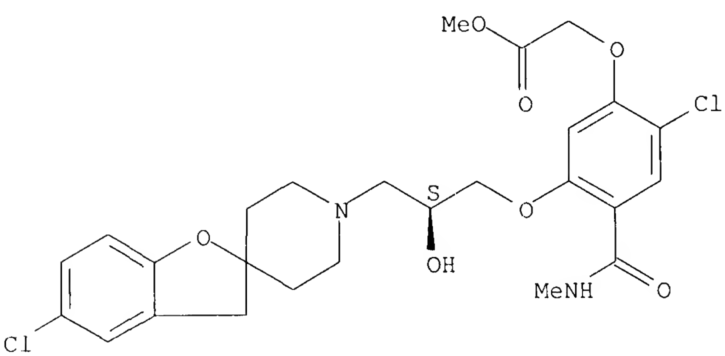
CN Acetamide, N-[5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



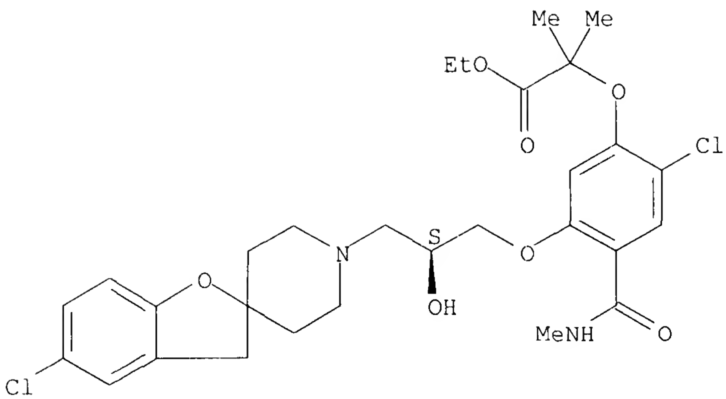
RN 1003567-27-8 CAPLUS
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 1003567-28-9 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



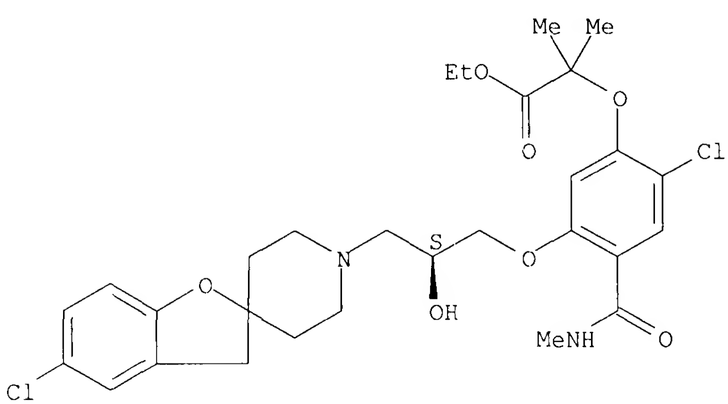
RN 1003567-29-0 CAPLUS

CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(methylamino)carbonyl]phenoxy]-2-methyl-, ethyl ester, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

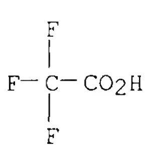
CRN 1003567-28-9
CMF C29 H36 Cl2 N2 O7

Absolute stereochemistry.



CM 2

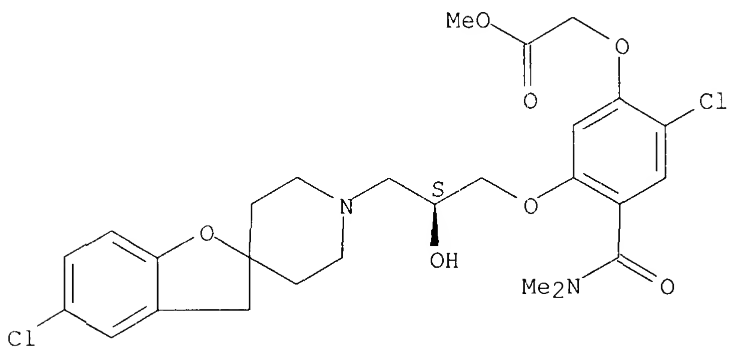
CRN 76-05-1
CMF C2 H F3 O2



10/579,545

RN 1003567-33-6 CAPLUS
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.

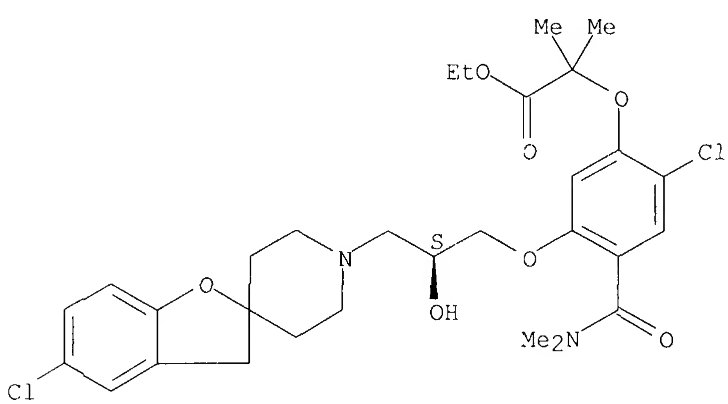


RN 1003567-35-8 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, ethyl ester, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

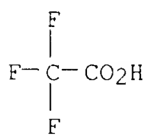
CRN 1003567-34-7
CMF C30 H38 Cl2 N2 O7

Absolute stereochemistry.



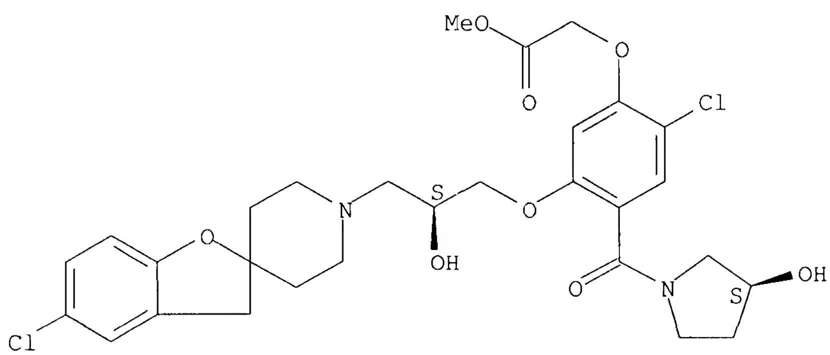
CM 2

CRN 76-05-1
CMF C2 H F3 O2

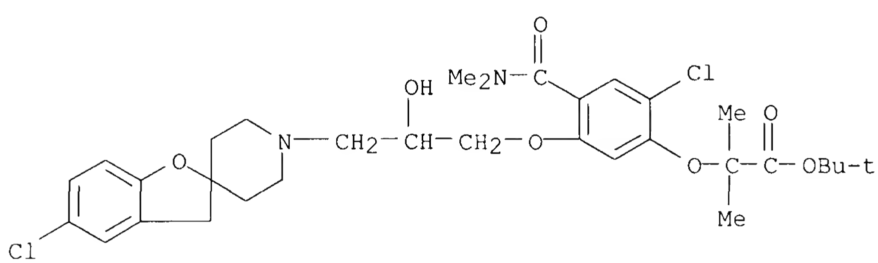


RN 1003567-36-9 CAPLUS
CN Acetic acid, 2-[2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[[(3S)-3-hydroxy-1-pyrrolidinyl]carbonyl]phenoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 1003567-37-0 CAPLUS
CN Propanoic acid, 2-[2-chloro-5-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(dimethylamino)carbonyl]phenoxy]-2-methyl-, 1,1-dimethylethyl ester (CA INDEX NAME)

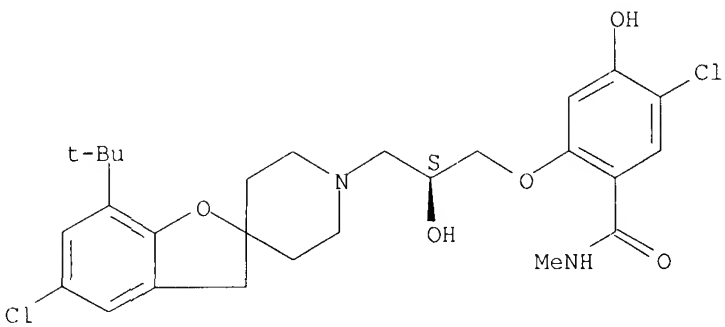


RN 1003567-43-8 CAPLUS
CN Benzamide, 5-chloro-2-[(2S)-3-[5-chloro-7-(1,1-dimethylethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]-2-hydroxypropoxy]-4-hydroxy-N-methyl-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

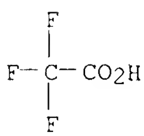
CRN 1003567-42-7
CMF C27 H34 Cl2 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:588965 CAPLUS
DOCUMENT NUMBER: 143:115452
TITLE: Preparation of tricyclic spiropiperidines as modulators of chemokine receptor activity
INVENTOR(S): Hossain, Nafizal; Ivanova, Svetlana
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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CA 2548494	A1	20050707	CA 2004-2548494		20041220
EP 1699791	A1	20060913	EP 2004-809111		20041220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR, IS					
BR 2004017036	A	20070206	BR 2004-17036		20041220
CN 1918160	A	20070221	CN 2004-80042013		20041220
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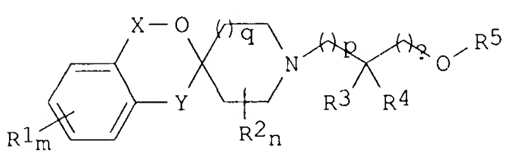
MX 2006PA07025	A	20060831	MX 2006-PA7025		20060619
US 2007099945	A1	20070503	US 2006-583468		20060620
IN 2006MN00848	A	20070518	IN 2006-MN848		20060718
NO 2006003355	A	20060922	NO 2006-3355		20060719
PRIORITY APPLN. INFO.:			SE 2003-3541	A	20031222
			WO 2004-SE1938	W	20041220

OTHER SOURCE(S): CASREACT 143:115452; MARPAT 143:115452

GI



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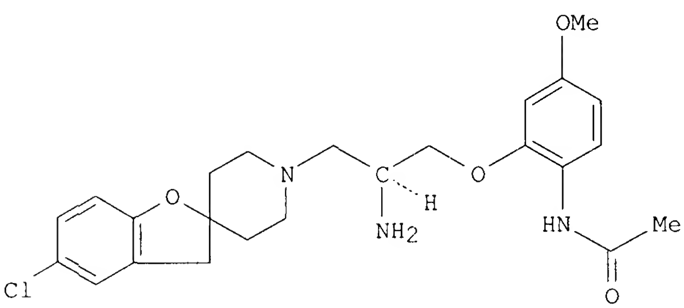


II

AB Title compds. I [m = 0-4; R1 = halo, CN, OH, etc.; X = bond, CH2 and Y = bond, CH2 provided that X, Y do not both simultaneously represent bond, CH2; n = 0-2; R2 = halo, alkyl, haloalkyl; q = 0-1; p = 0-2; R3 = halo, amino, carboxyl, etc.; R4 = H, alkyl, haloalkyl, halo; a = 0-2 provided that p and a are not both 0; R5 = (un)saturated 5-10-membered ring system] are prepared For instance, II is prepared in 4 steps from 5-methoxy-2-nitrophenol, (S)-oxiran-2-ylmethanol, and 5-chlorospiro[3H-benzofuran-2,4'-piperidine] (preparation given). I are modulators of chemokine receptor activity [no data] and useful for the treatment of, e.g., rheumatoid arthritis.

IT 644968-75-2P, N-[2-[[(2S)-3-(5-Chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-hydroxyphenyl]acetamide 644971-08-4P, Methyl 5-chloro-2-[[(2S)-3-(5-chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate trifluoroacetate 644971-09-5P, 5-Chloro-2-[[(2S)-3-(5-chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride

644972-75-8P, N-[2-[[(2R)-3-(5-Fluorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methoxyphenyl]acetamide 857264-41-6P, (R)-1-(5-Chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-methoxy-2-nitrophenoxy)propan-2-ol 857264-42-7P, N-[2-[[(2R)-3-(5-Chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-methoxyphenyl]acetamide 857264-49-4P, (R)-1-(5-Methoxy-2-nitrophenoxy)-3-(spiro[3H-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol 857264-50-7P, N-[2-[[(2R)-2-Hydroxy-3-(spiro[3H-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy]-4-methoxyphenyl]acetamide 857264-62-1P, N-[2-[[(2R)-3-(5-Chlorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]phenyl]urea 857264-65-4P, N-[2-[[(2R)-3-(5-Fluorospiro[3H-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]phenyl]urea

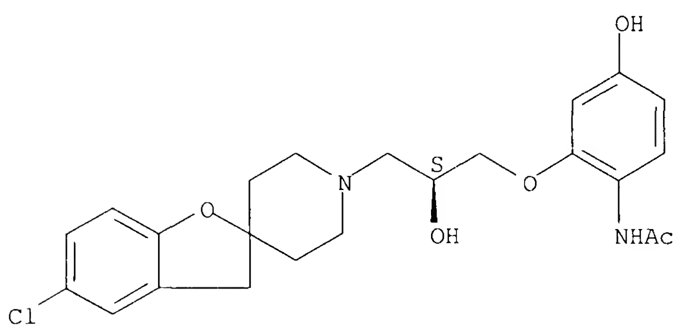
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of tricyclic spiropiperidines as modulators of chemokine receptor activity)

RN 644968-75-2 CAPLUS

CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



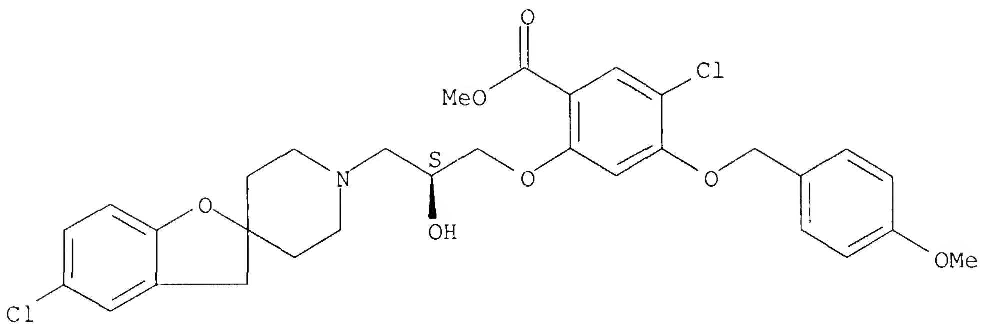
RN 644971-08-4 CAPLUS

CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

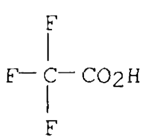
CRN 644971-07-3
CMF C31 H33 Cl2 N O7

Absolute stereochemistry.



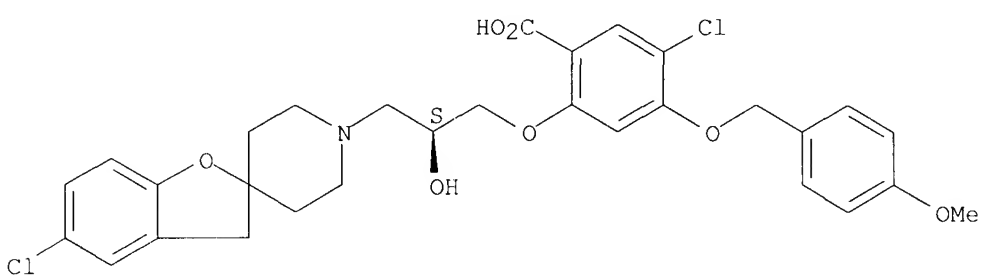
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644971-09-5 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

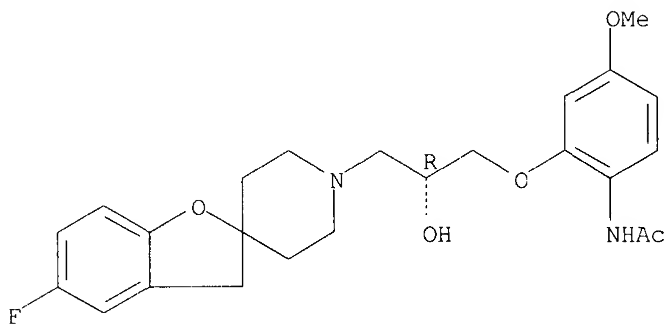
Absolute stereochemistry.



● HCl

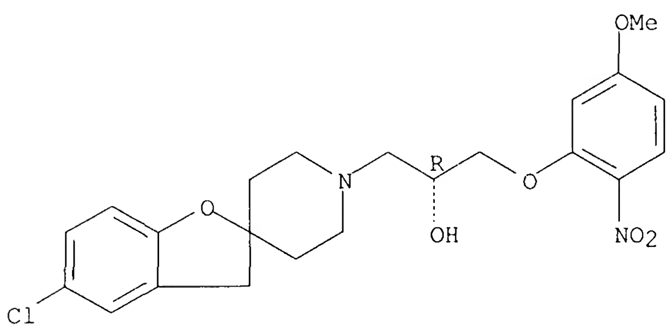
RN 644972-75-8 CAPLUS
CN Acetamide, N-[2-[(2R)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



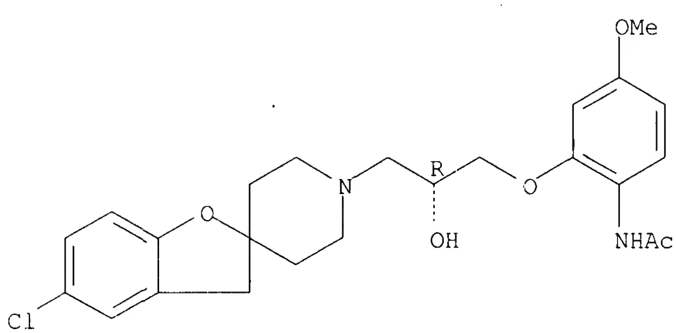
RN 857264-41-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(5-methoxy-2-nitrophenoxy)methyl]-, (αR)- (CA INDEX NAME)

Absolute stereochemistry.



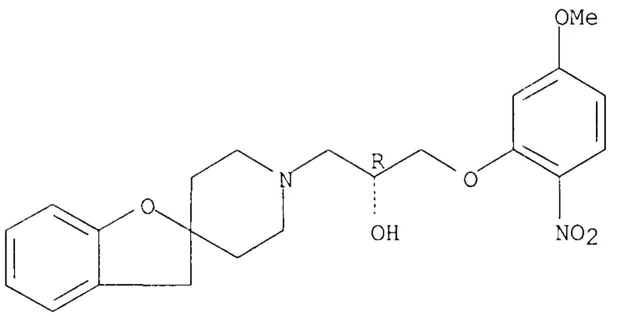
RN 857264-42-7 CAPLUS
CN Acetamide, N-[2-[(2R)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



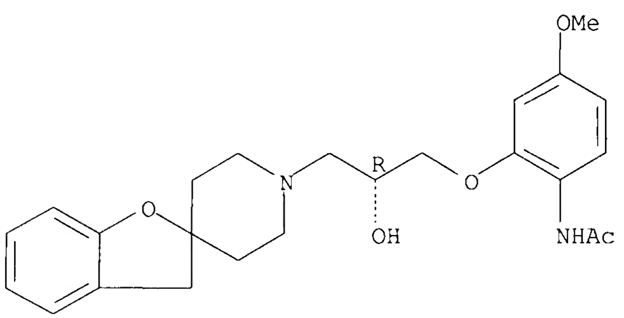
RN 857264-49-4 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(5-methoxy-2-nitrophenoxy)methyl]-, (αR)- (CA INDEX NAME)

Absolute stereochemistry.



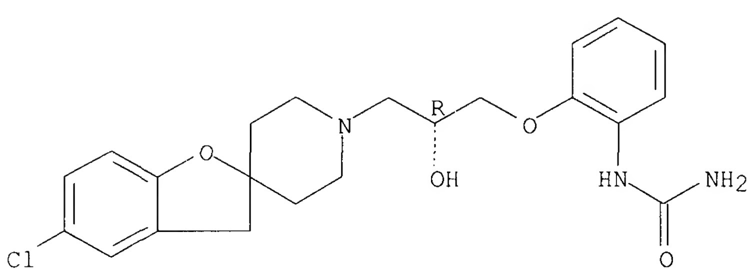
RN 857264-50-7 CAPLUS
CN Acetamide, N-[2-[(2R)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-4-methoxyphenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



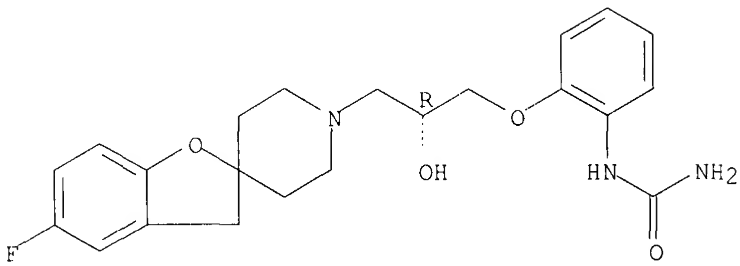
RN 857264-62-1 CAPLUS
CN Urea, [2-[(2R)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 857264-65-4 CAPLUS
CN Urea, [2-[(2R)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:472162 CAPLUS
DOCUMENT NUMBER: 143:26501
TITLE: Preparation of N-(3-phenoxy-2-hydroxypropyl)-tricyclic spiropiperidine derivatives as modulators of chemokine receptor activity
INVENTOR(S): Baxter, Andrew; Hossain, Nafizal; Ivanova, Svetlana; Mensonides-Harsema, Marguerite; Pimm, Austen; Reuberson, James
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

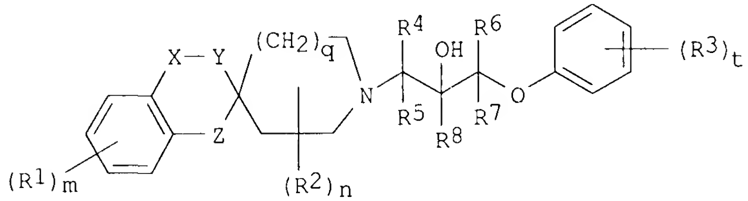
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005049620	A1	20050602	WO 2004-SE1658	20041115
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004291455	A1	20050602	AU 2004-291455	20041115
AU 2004291455	B2	20080124		
CA 2546028	A1	20050602	CA 2004-2546028	20041115
EP 1687311	A1	20060809	EP 2004-800321	20041115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR, IS				
BR 2004016745	A	20070116	BR 2004-16745	20041115
CN 1906200	A	20070131	CN 2004-80040642	20041115
JP 2007512323	T	20070517	JP 2006-541084	20041115
MX 2006PA05427	A	20060719	MX 2006-PA5427	20060512
US 2007129393	A1	20070607	US 2006-579545	20060516
IN 2006DN03354	A	20070824	IN 2006-DN3354	20060609
NO 2006002900	A	20060821	NO 2006-2900	20060620

10/579,545

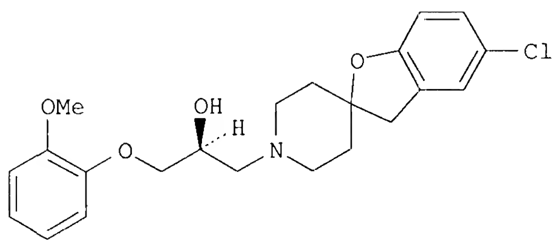
PRIORITY APPLN. INFO.: SE 2003-3090 A 20031120
WO 2004-SE1658 W 20041115

OTHER SOURCE(S): MARPAT 143:26501

GI



I



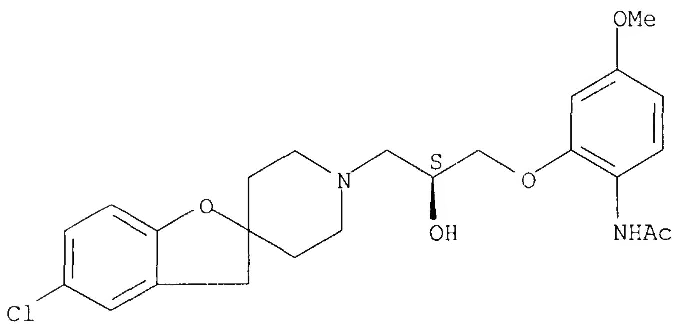
II

AB The invention provides compds. of formula (I) [wherein m = 0-4; R1 = halogen, cyano, HO, C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, sulfonamido; X = a bond, CH2, O; Y = a bond, CH2, O; Z = a bond, O, NH, CH2; provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent O; n = 0-2; R2 = halogen, C1-6 alkyl, C1-6 haloalkyl; q = 0, 1; t = 0-5; R3 = halogen, cyano, NO2, HO, CHO, NR9R10, CH2COR11R12, NHSO2R13R14, CH2R17, C1-6 alkylcarbonyl, phenylcarbonyl, C3-6 cycloalkyl, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, Ph, (un)substituted and (un)saturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from N, O, and S; R4-R8 = H, halogen, C1-6 alkyl, C1-6 haloalkyl; R9, R10, R13, R14, R15, R16 = H, C1-6 alkyl; R11, R12 = H, C1-6 alkyl; or NR11R12 or NR15R16 together form (un)substituted 4- to 7-membered saturated heterocyclic ring; R17 = ≥1 oxo-(un)substituted 5 to 7 membered saturated heterocyclic ring containing at least one N atom] or pharmaceutically acceptable salts or solvates thereof. These compds. modulate chemokine receptor activity (no data) and are useful in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial, including rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, and multiple sclerosis. Thus, a mixture of 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.67 mmol) and (2S)-2-[(2-methoxyphenoxy)methyl]oxirane (121 mg, 0.67 mmol) in ethanol (2 mL) was stirred at 80° overnight to give, after evaporation of the solvent and purification on silica gel chromatog., (2S)-1-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(2-methoxyphenoxy)propan-2-ol hydrochloride (II).

IT 644968-71-8P 644968-75-2P 644970-61-6P
852951-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of N-(3-phenoxy-2-hydroxypropyl)spiropiperidine derivs. as modulators of chemokine receptor activity)

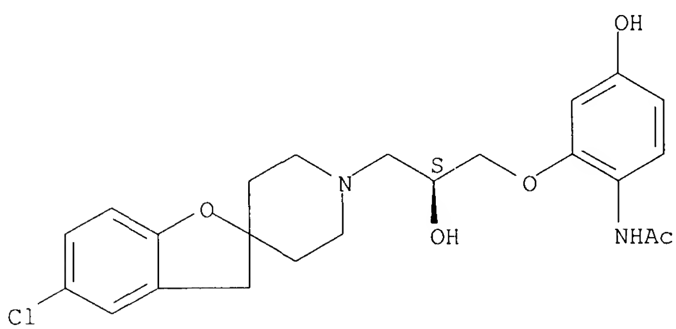
RN 644968-71-8 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644968-75-2 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.

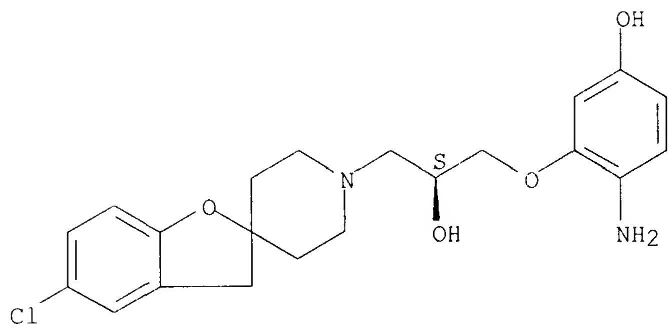


RN 644970-61-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-amino-5-hydroxyphenoxy)methyl]-5-chloro-, (αS)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

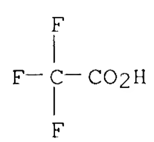
CRN 644970-60-5
CMF C21 H25 Cl N2 O4

Absolute stereochemistry.



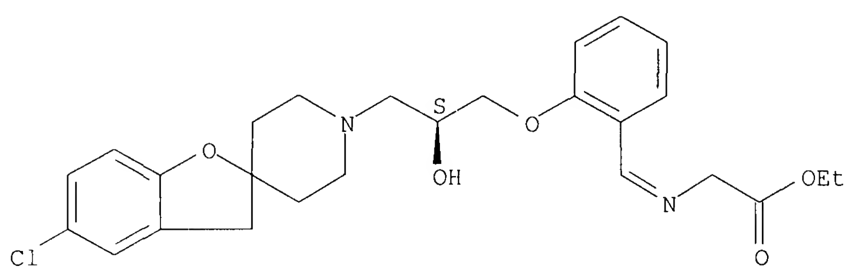
CM 2

CRN 76-05-1
CMF C2 H F3 O2



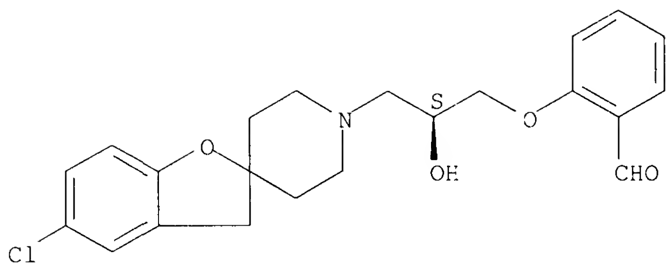
RN 852951-53-2 CAPLUS
CN Glycine, N-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]methylene]-, ethyl ester (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



IT 852950-88-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of N-(3-phenoxy-2-hydroxypropyl)spiropiperidine derivs. as modulators of chemokine receptor activity)
RN 852950-88-0 CAPLUS
CN Benzaldehyde, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]- (CA INDEX NAME)

Absolute stereochemistry.



IT 852950-60-8P 852950-61-9P 852950-62-0P
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852950-71-1P 852950-73-3P 852950-75-5P
852950-77-7P 852950-78-8P 852950-79-9P
852950-80-2P 852950-81-3P 852950-82-4P
852950-83-5P 852950-84-6P 852950-85-7P
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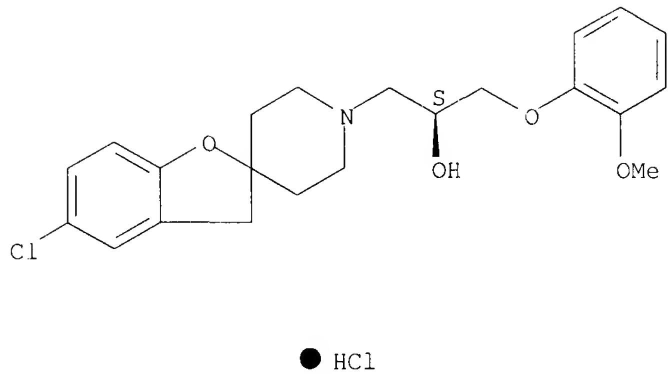
852951-36-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-(3-phenoxy-2-hydroxypropyl)spiropiperidine derivs. as modulators of chemokine receptor activity)

RN 852950-60-8 CAPLUS

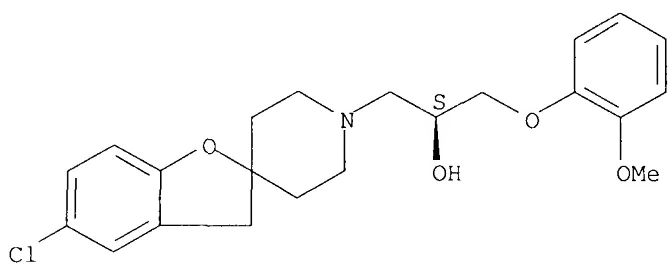
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-methoxyphenoxy)methyl]-, hydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



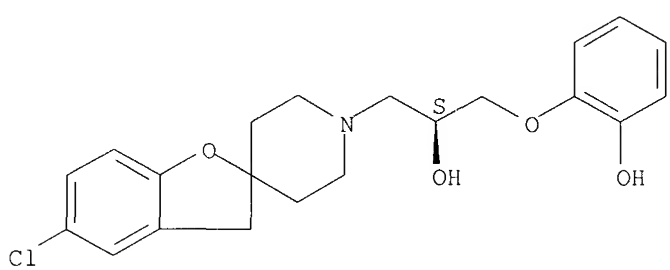
RN 852950-61-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-methoxyphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



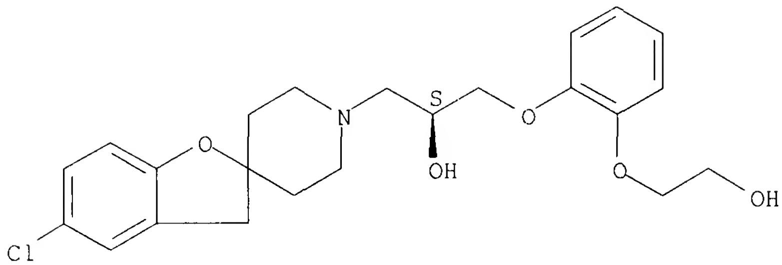
RN 852950-62-0 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-hydroxyphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



RN 852950-63-1 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(2-hydroxyethoxy)phenoxy]methyl]-, hydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

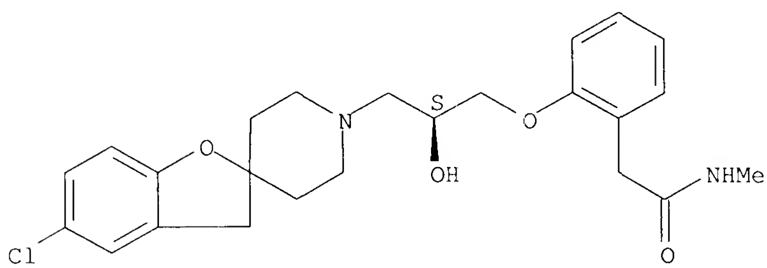


RN 852950-65-3 CAPLUS
CN Benzeneacetamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-methyl-, (αS)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

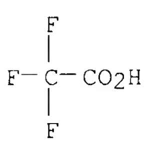
CRN 852950-64-2
CMF C24 H29 Cl N2 O4

Absolute stereochemistry.



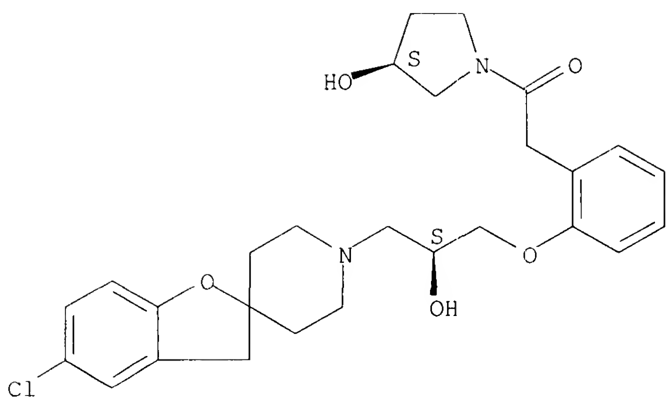
CM 2

CRN 76-05-1
CMF C2 H F3 O2



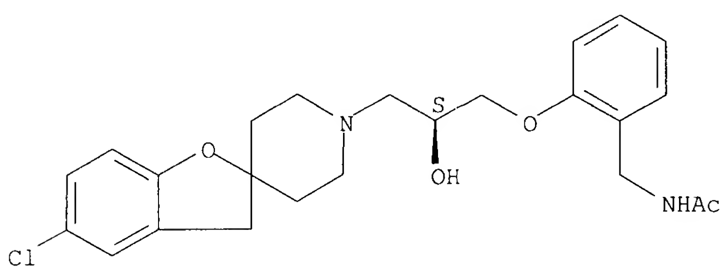
RN 852950-66-4 CAPLUS
CN 3-Pyrrolidinol, 1-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]acetyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



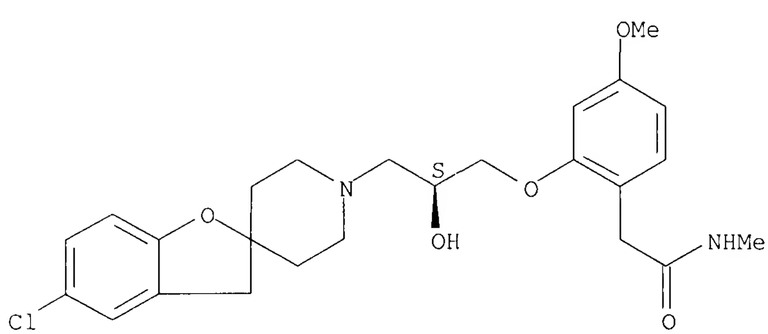
RN 852950-67-5 CAPLUS
CN Acetamide, N-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 852950-68-6 CAPLUS
CN Benzeneacetamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

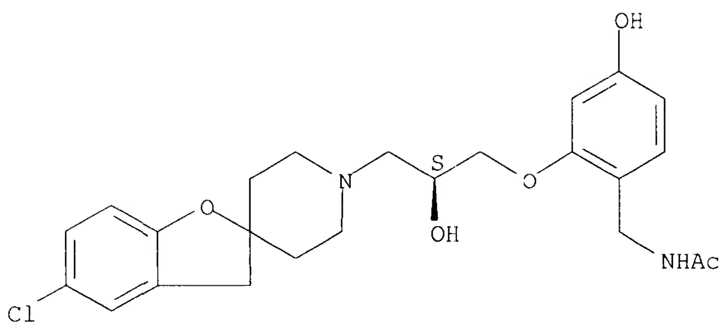


RN 852950-70-0 CAPLUS
CN Acetamide, N-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]methyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

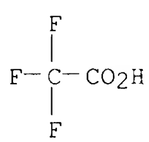
CRN 852950-69-7
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



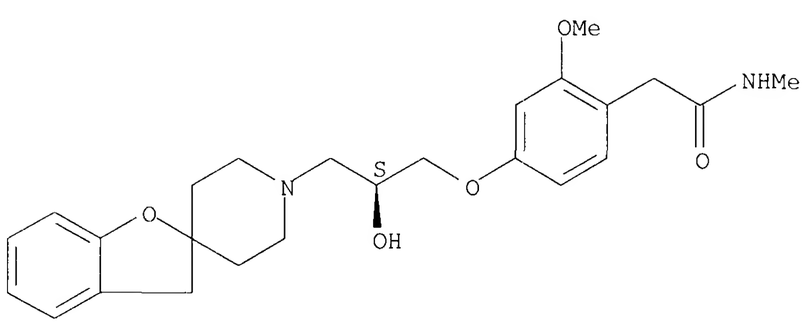
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 852950-71-1 CAPLUS
CN Benzeneacetamide, 4-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-2-methoxy-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

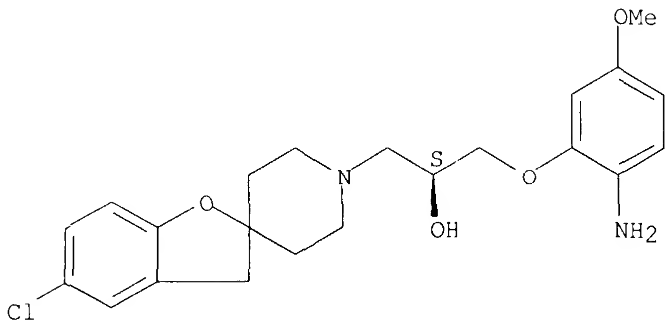


RN 852950-73-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-amino-5-methoxyphenoxy)methyl]-5-chloro-, (αS)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

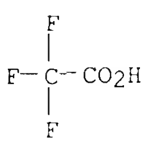
CRN 852950-72-2
CMF C22 H27 Cl N2 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

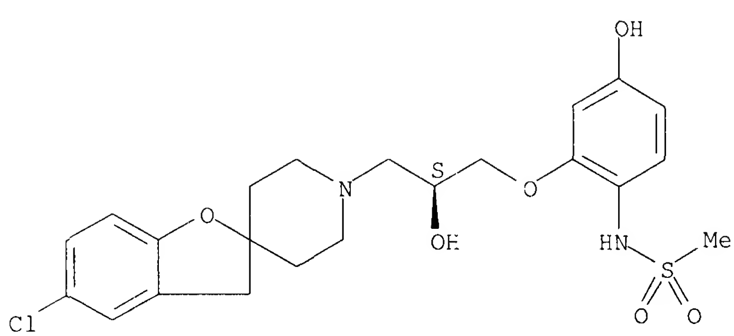


RN 852950-75-5 CAPLUS
CN Methanesulfonamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

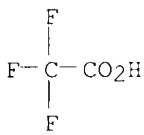
CRN 852950-74-4
CMF C22 H27 Cl N2 O6 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

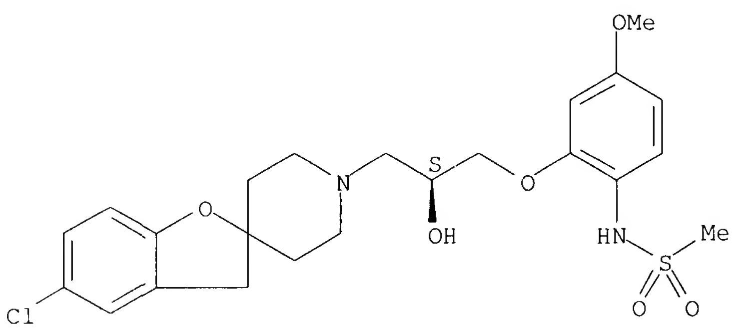


RN 852950-77-7 CAPLUS
CN Methanesulfonamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

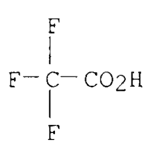
CRN 852950-76-6
CMF C23 H29 Cl N2 O6 S

Absolute stereochemistry.



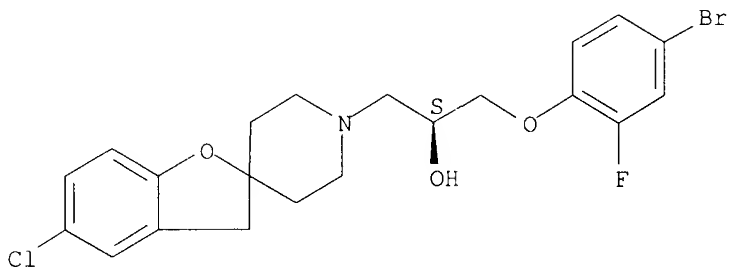
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 852950-78-8 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(4-bromo-2-fluorophenoxy)methyl]-5-chloro-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.

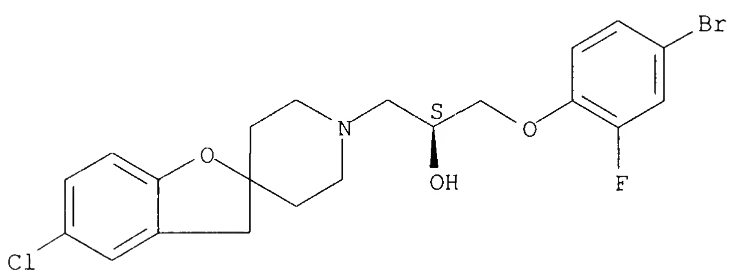


RN 852950-79-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(4-bromo-2-fluorophenoxy)methyl]-5-chloro-, (αS)-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

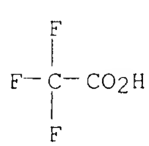
CRN 852950-78-8
CMF C21 H22 Br Cl F N O3

Absolute stereochemistry.



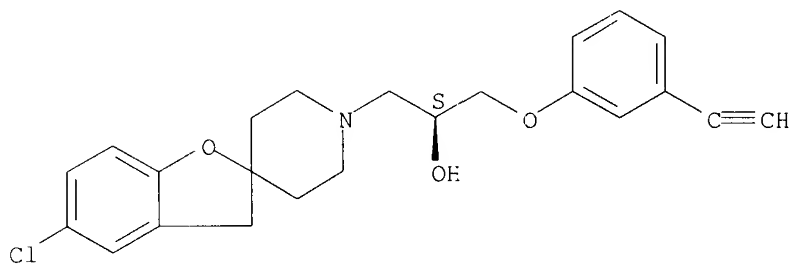
CM 2

CRN 76-05-1
CMF C2 H F3 O2



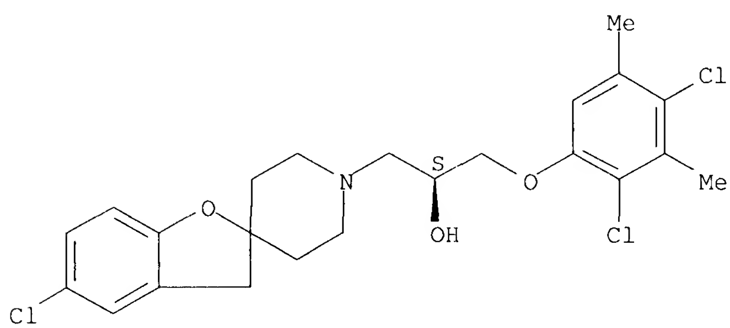
RN 852950-80-2 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(3-ethynylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



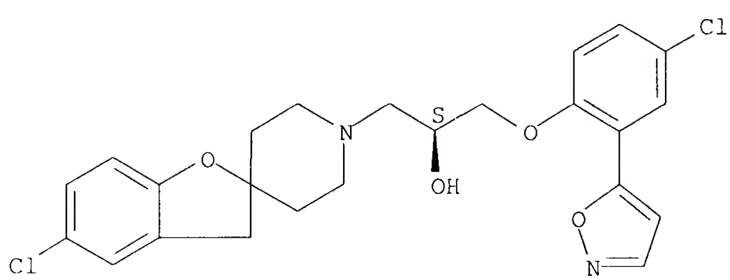
RN 852950-81-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,4-dichloro-3,5-dimethylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



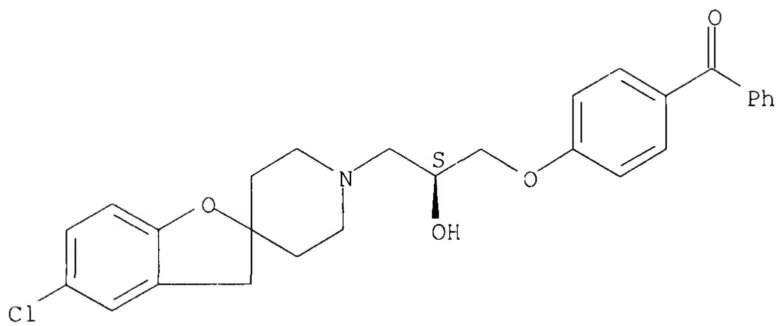
RN 852950-82-4 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[4-chloro-2-(5-isoxazolyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



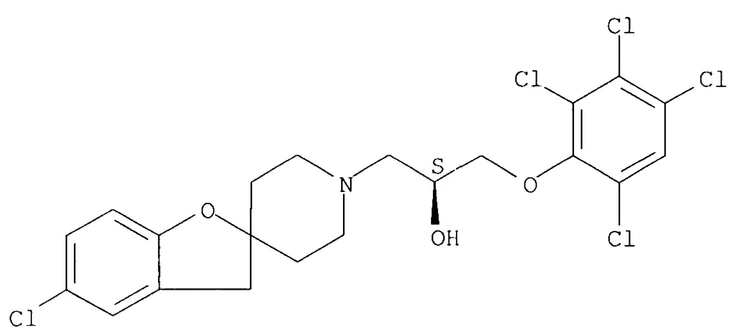
RN 852950-83-5 CAPLUS
CN Methanone, [4-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]phenyl- (CA INDEX NAME)

Absolute stereochemistry.



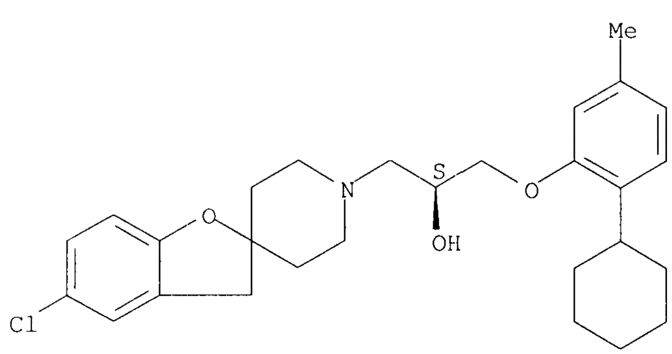
RN 852950-84-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,3,4,6-tetrachlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



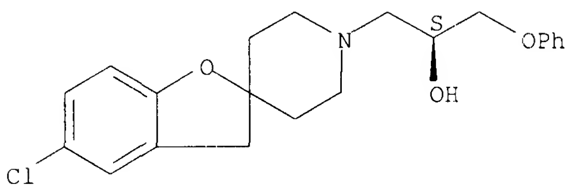
RN 852950-85-7 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-cyclohexyl-5-methylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



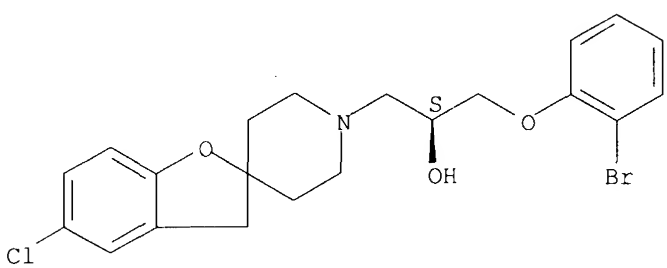
RN 852950-86-8 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-(phenoxymethyl)-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



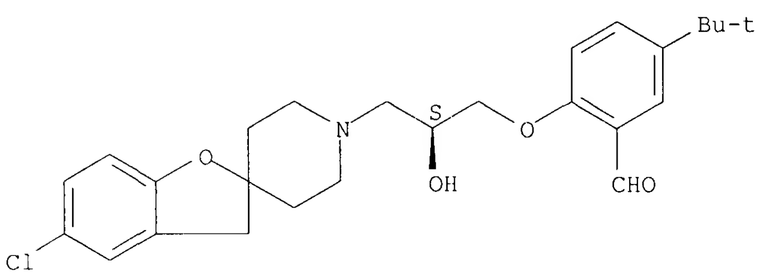
RN 852950-87-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-bromophenoxy)methyl]-5-chloro-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



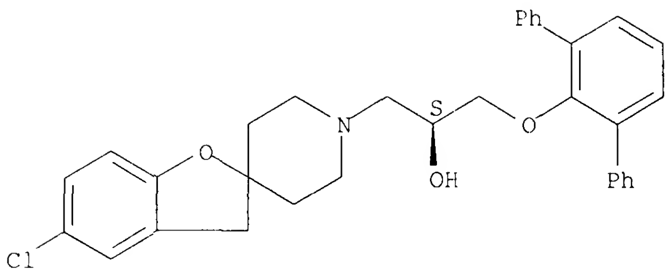
RN 852950-89-1 CAPLUS
CN Benzaldehyde, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-(1,1-dimethylethyl)- (CA INDEX NAME)

Absolute stereochemistry.



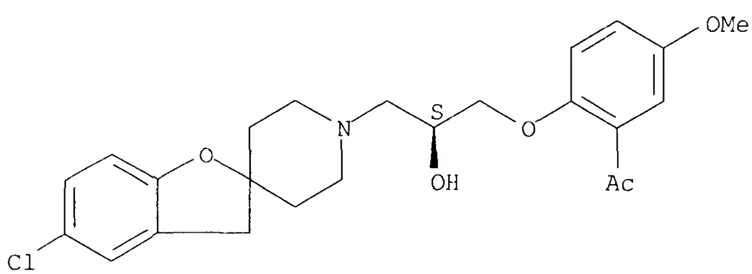
RN 852950-90-4 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[([1,1':3',1''-terphenyl]-2'-yloxy)methyl]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



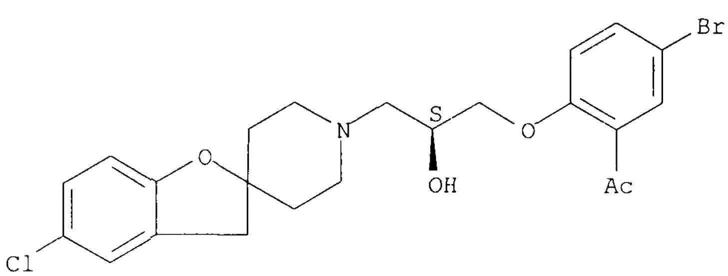
RN 852950-91-5 CAPLUS
CN Ethanone, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



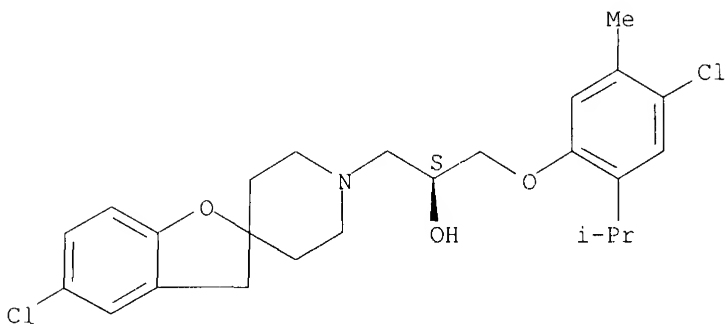
RN 852950-92-6 CAPLUS
CN Ethanone, 1-[5-bromo-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



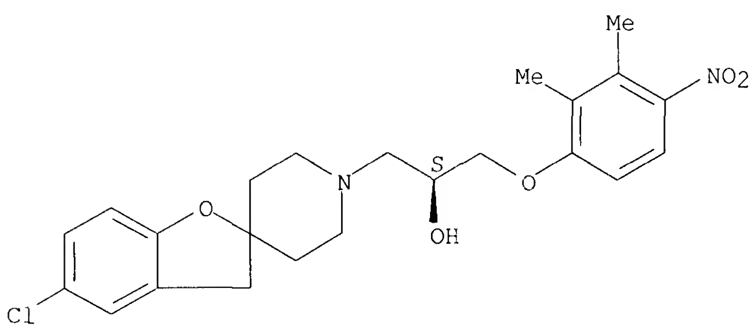
RN 852950-93-7 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[4-chloro-5-methyl-2-(1-methylethyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



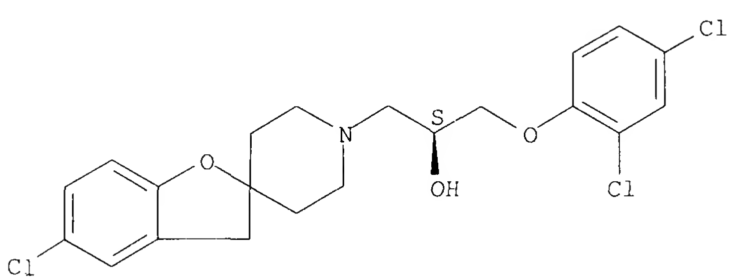
RN 852950-94-8 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,3-dimethyl-4-nitrophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



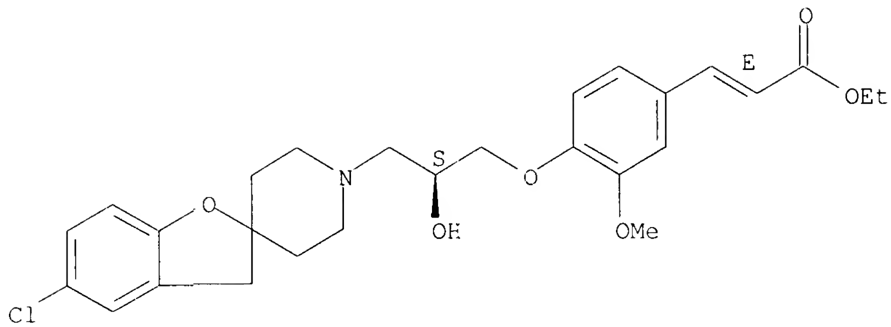
RN 852950-95-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,4-dichlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



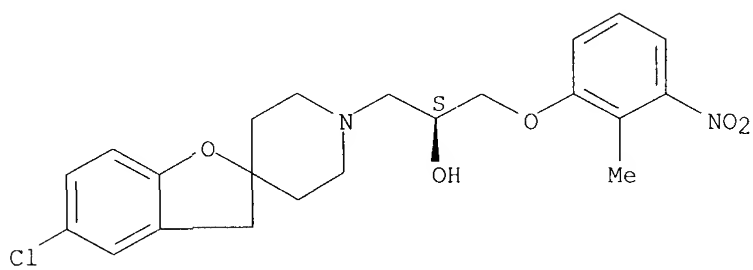
RN 852950-96-0 CAPLUS
CN 2-Propenoic acid, 3-[4-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-3-methoxyphenyl]-, ethyl ester, (2E)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



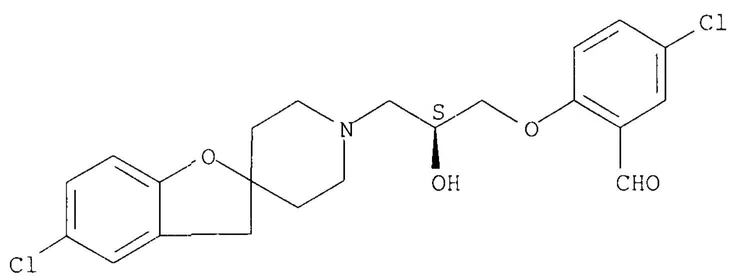
RN 852950-97-1 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-methyl-3-nitrophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



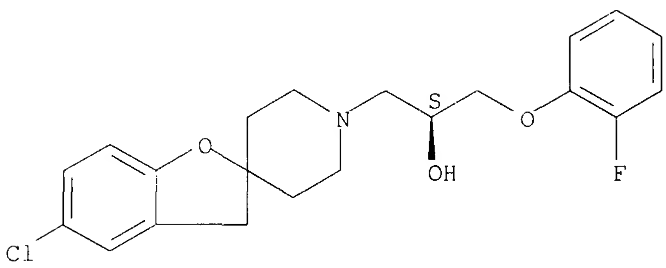
RN 852950-98-2 CAPLUS
CN Benzaldehyde, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]- (CA INDEX NAME)

Absolute stereochemistry.



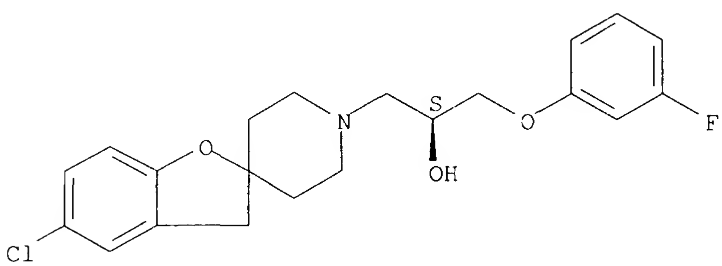
RN 852950-99-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-fluorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



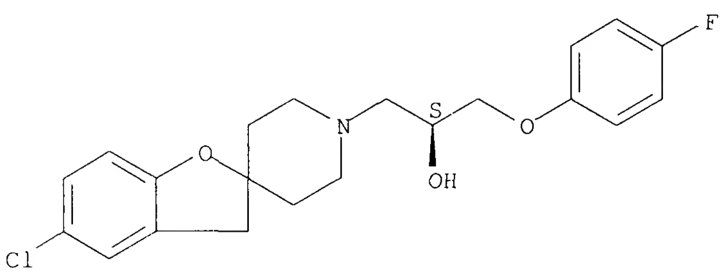
RN 852951-00-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(3-fluorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



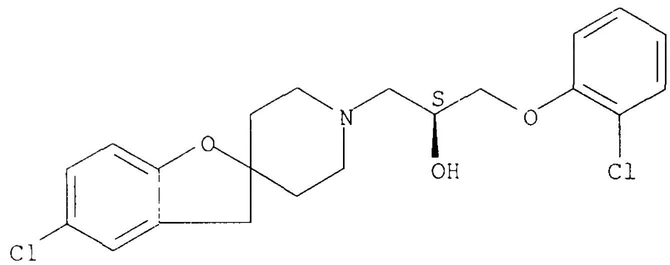
RN 852951-01-0 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(4-fluorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



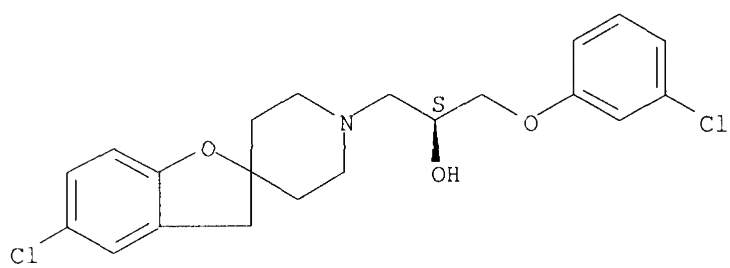
RN 852951-02-1 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-chlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



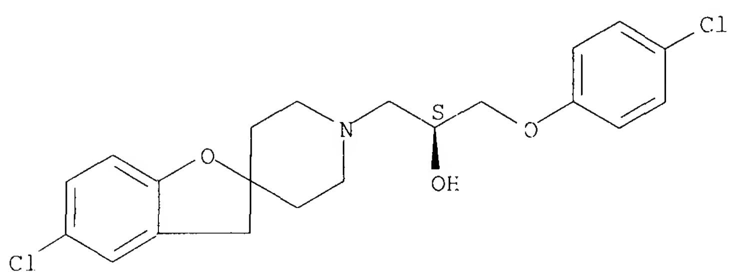
RN 852951-03-2 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(3-chlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



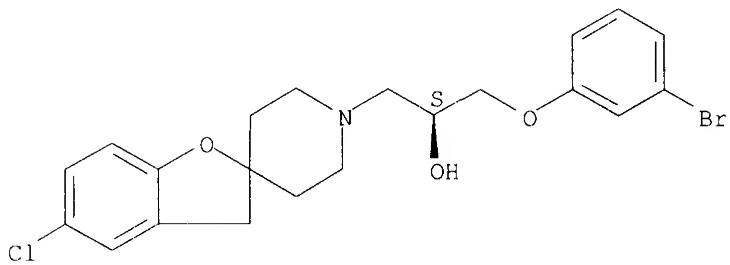
RN 852951-04-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(4-chlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



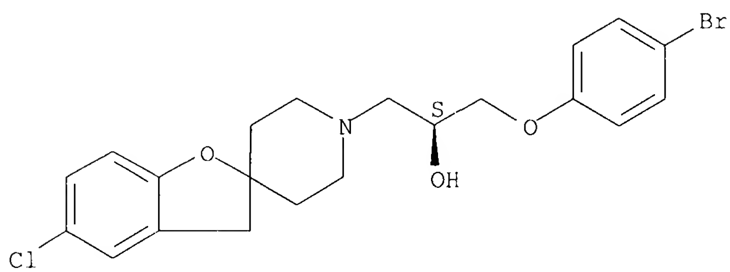
RN 852951-05-4 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(3-bromophenoxy)methyl]-5-chloro-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



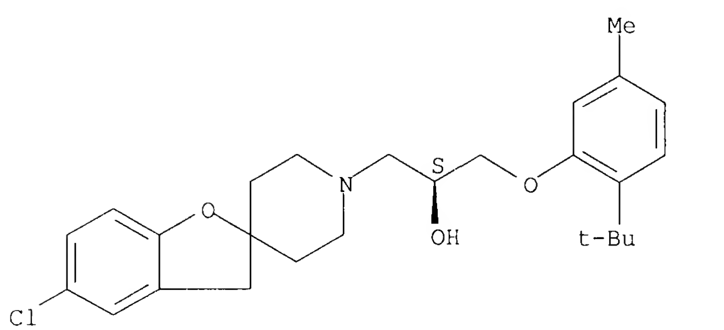
RN 852951-06-5 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(4-bromophenoxy)methyl]-5-chloro-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



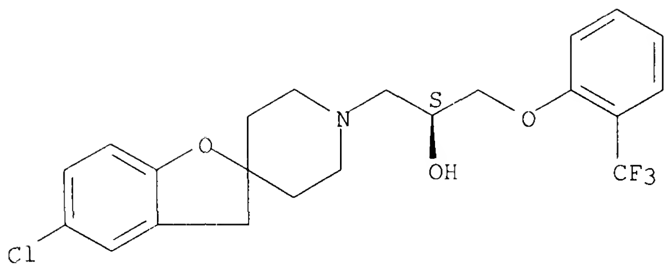
RN 852951-07-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(1,1-dimethylethyl)-5-methylphenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



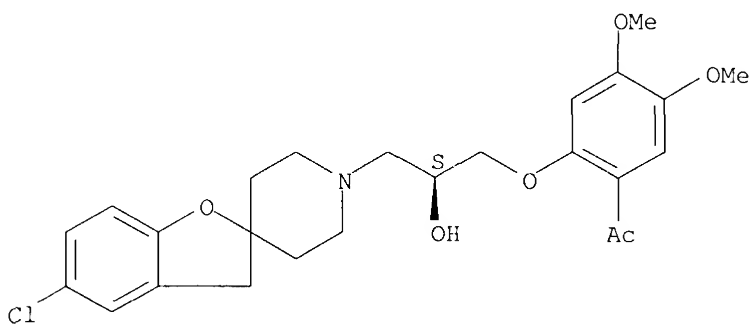
RN 852951-08-7 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(trifluoromethyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



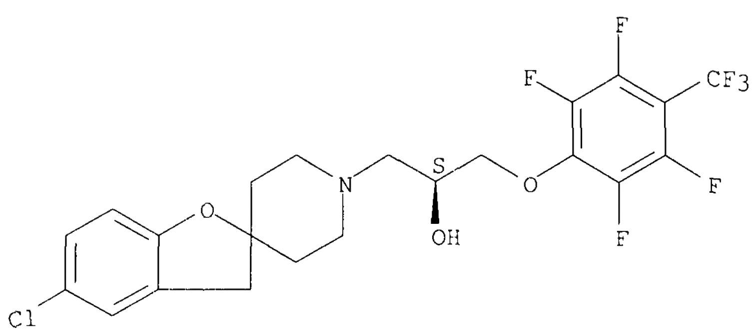
RN 852951-09-8 CAPLUS
CN Ethanone, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4,5-dimethoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



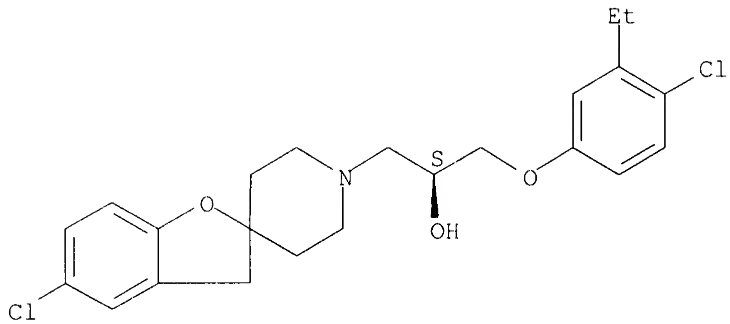
RN 852951-10-1 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



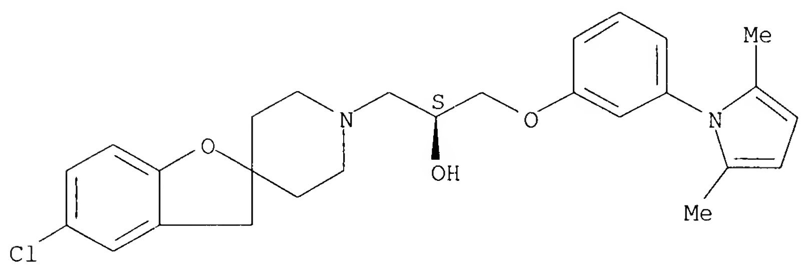
RN 852951-11-2 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(4-chloro-3-ethylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



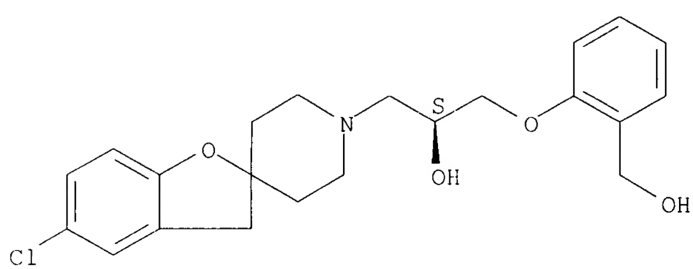
RN 852951-12-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[3-(2,5-dimethyl-1H-pyrrol-1-yl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



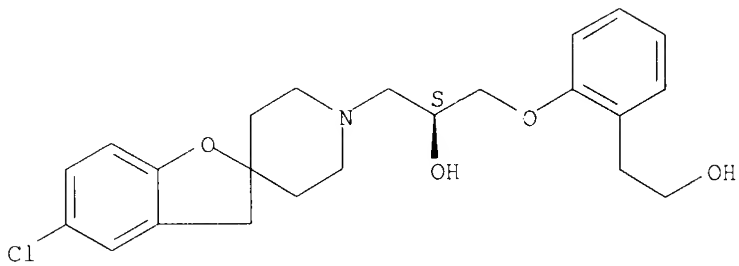
RN 852951-13-4 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(hydroxymethyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



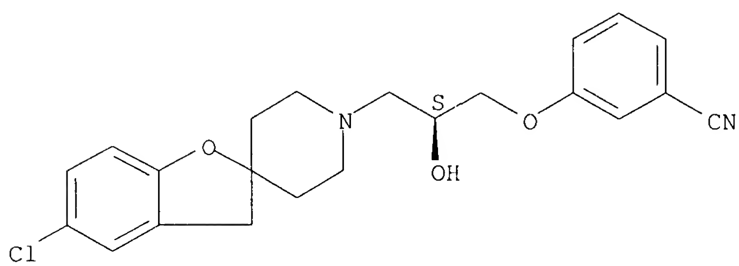
RN 852951-14-5 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(2-hydroxyethyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



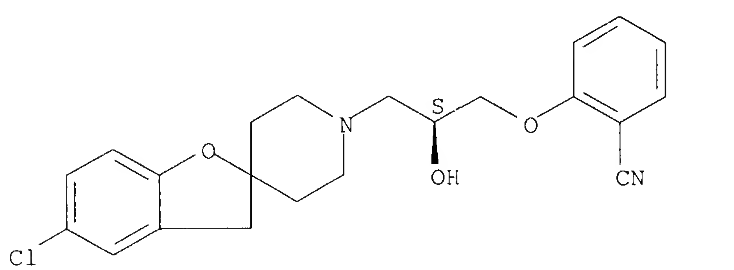
RN 852951-15-6 CAPLUS
CN Benzonitrile, 3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]- (CA INDEX NAME)

Absolute stereochemistry.



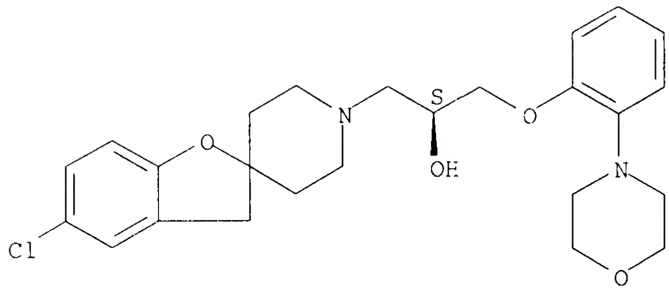
RN 852951-16-7 CAPLUS
CN Benzonitrile, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]- (CA INDEX NAME)

Absolute stereochemistry.



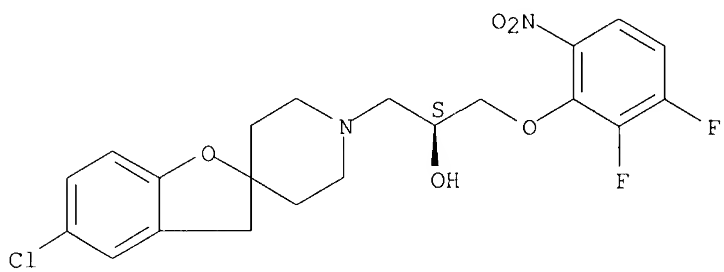
RN 852951-17-8 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(4-morpholinyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



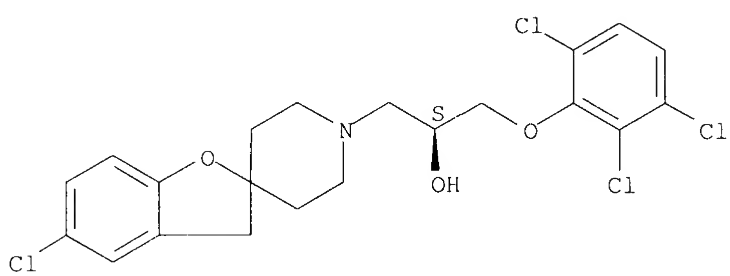
RN 852951-18-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,3-difluoro-6-nitrophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



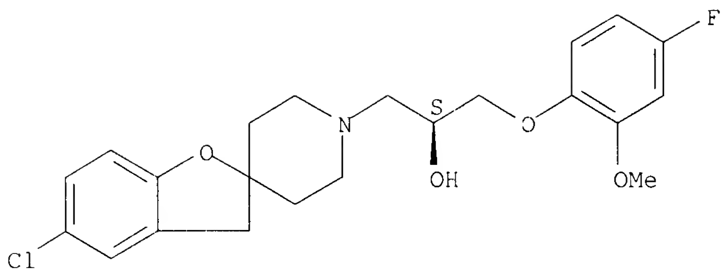
RN 852951-19-0 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,3,6-trichlorophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



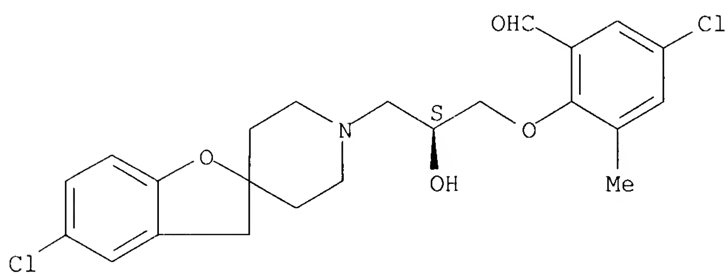
RN 852951-20-3 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(4-fluoro-2-methoxyphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



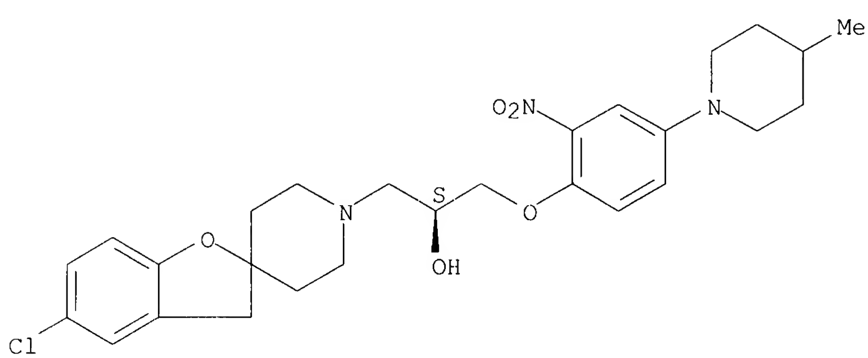
RN 852951-21-4 CAPLUS
CN Benzaldehyde, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-3-methyl- (CA INDEX NAME)

Absolute stereochemistry.



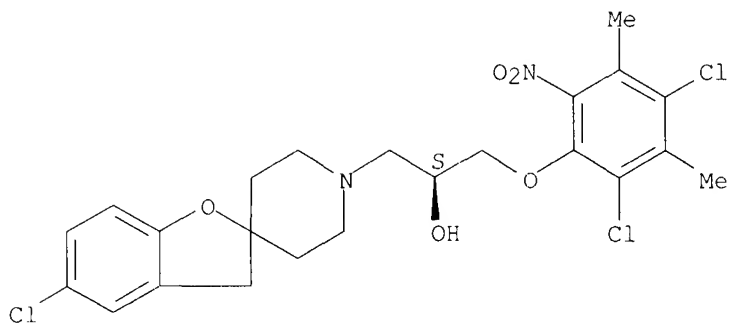
RN 852951-22-5 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[4-(4-methyl-1-piperidinyl)-2-nitrophenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



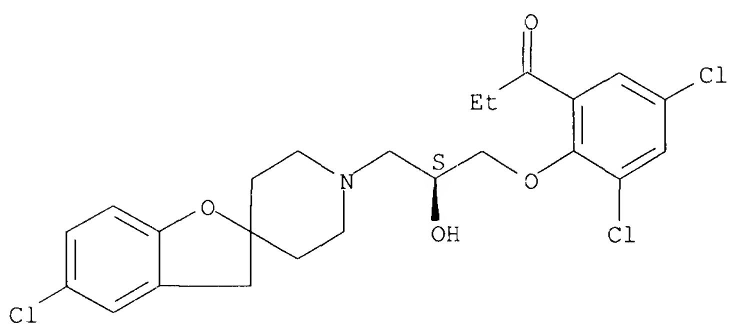
RN 852951-23-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2,4-dichloro-3,5-dimethyl-6-nitrophenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



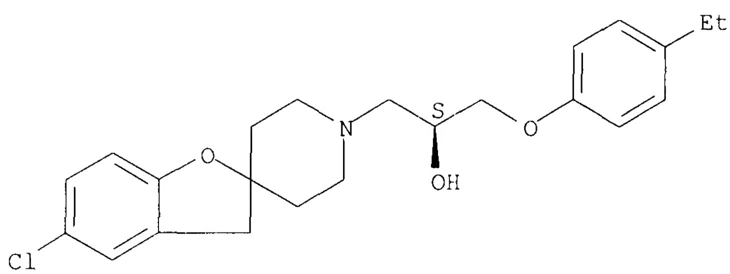
RN 852951-24-7 CAPLUS
CN 1-Propanone, 1-[3,5-dichloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



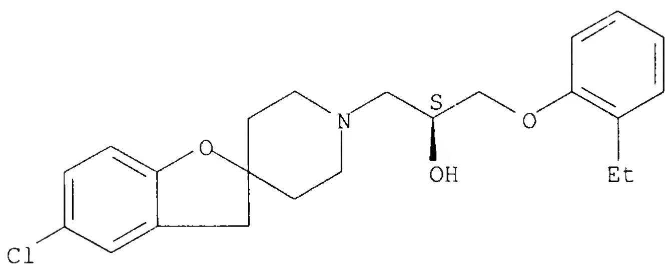
RN 852951-25-8 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(4-ethylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



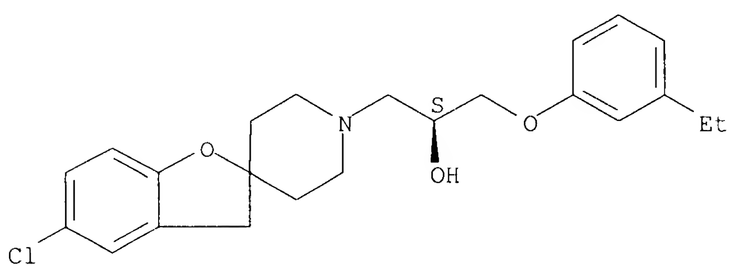
RN 852951-26-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(2-ethylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



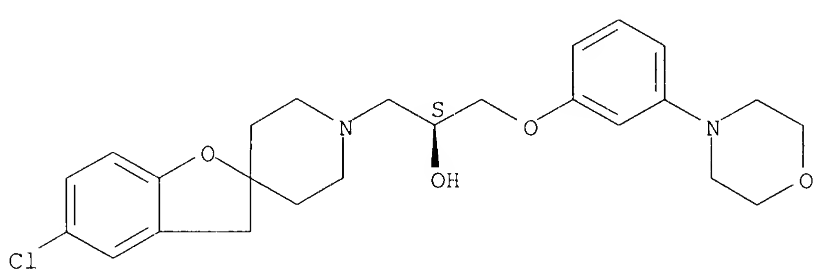
RN 852951-27-0 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[(3-ethylphenoxy)methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



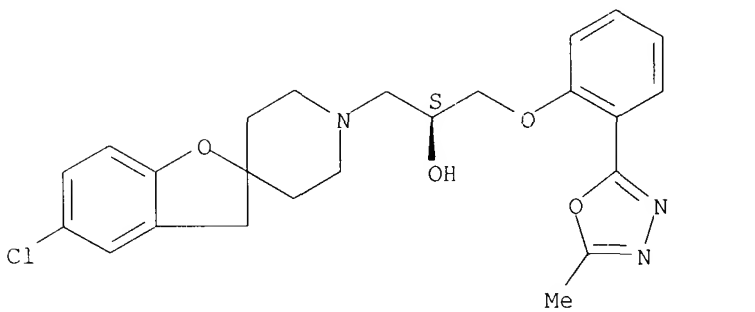
RN 852951-28-1 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[3-(4-morpholinyl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



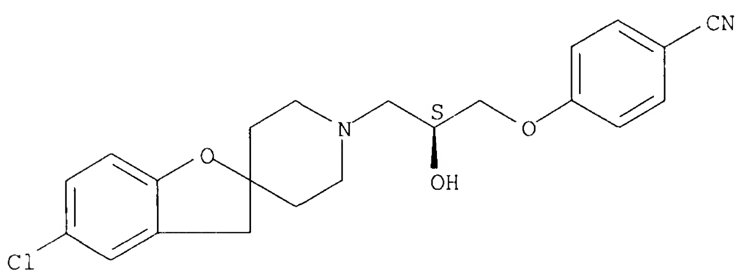
RN 852951-29-2 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, 5-chloro-α-[[2-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]methyl]-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



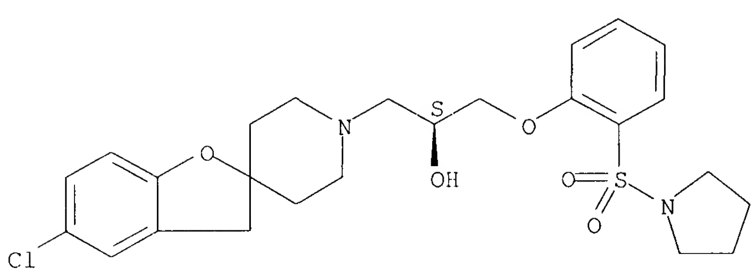
RN 852951-30-5 CAPLUS
CN Benzonitrile, 4-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]- (CA INDEX NAME)

Absolute stereochemistry.



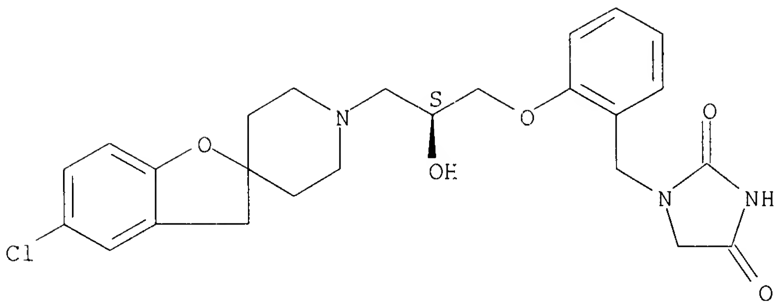
RN 852951-31-6 CAPLUS
CN Pyrrolidine, 1-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



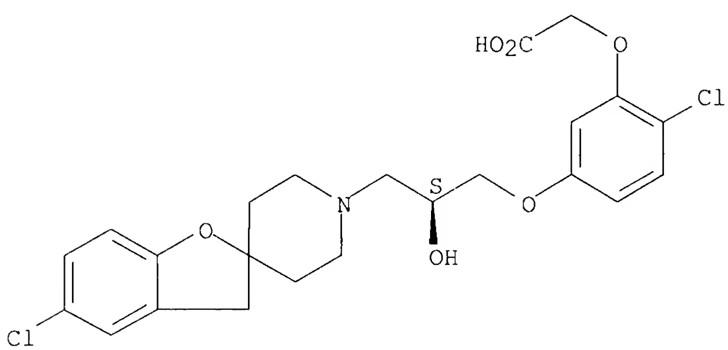
RN 852951-32-7 CAPLUS
CN 2,4-Imidazolidinedione, 1-[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



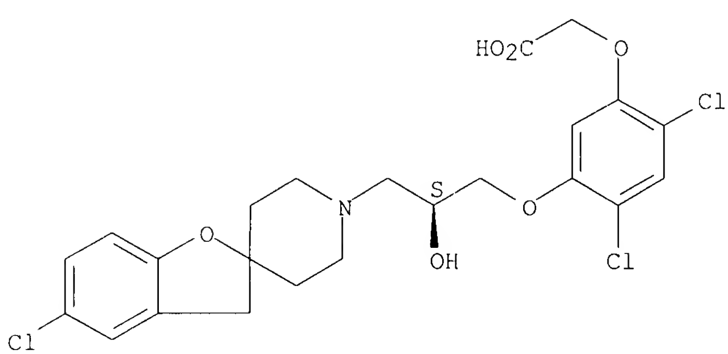
RN 852951-33-8 CAPLUS
CN Acetic acid, [2-chloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 852951-34-9 CAPLUS
CN Acetic acid, [2,4-dichloro-5-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

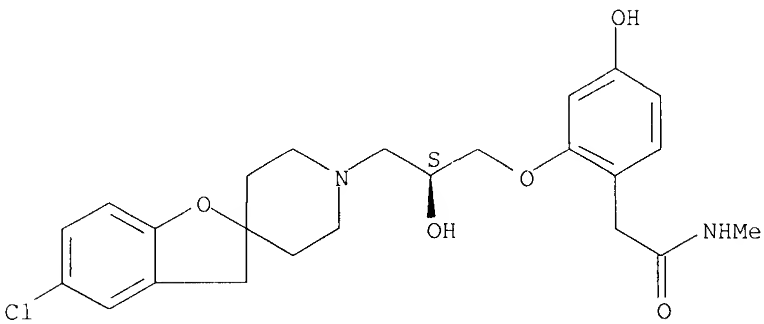


RN 852951-36-1 CAPLUS
CN Benzeneacetamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-methyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

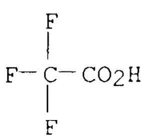
CRN 852951-35-0
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:41477 CAPLUS
DOCUMENT NUMBER: 140:93937
TITLE: Preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors
INVENTOR(S): Hossain, Nafizal; Ivanova, Svetlana; Mensonides-Harsema, Marguerite
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 281 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005295	A1	20040115	WO 2003-SE1185	20030707

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2492122	A1	20040115	CA 2003-2492122	20030707
AU 2003243122	A1	20040123	AU 2003-243122	20030707
EP 1521757	A1	20050413	EP 2003-762957	20030707
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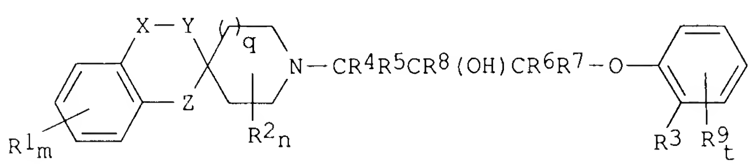
BR 2003012560	A	20050510	BR 2003-12560	20030707
CN 1675218	A	20050928	CN 2003-819146	20030707
JP 2005537255	T	20051208	JP 2004-519472	20030707
NZ 537259	A	20060831	NZ 2003-537259	20030707
CN 1974574	A	20070606	CN 2006-10143556	20030707
AT 385235	T	20080215	AT 2003-762957	20030707
IN 2004DN04014	A	20070427	IN 2004-DN4014	20041216
ZA 2005000024	A	20060222	ZA 2005-24	20050103
MX 2005PA00278	A	20050331	MX 2005-PA278	20050104
US 2005245741	A1	20051103	US 2005-520699	20050107
NO 2005000635	A	20050331	NO 2005-635	20050204

PRIORITY APPLN. INFO.: SE 2002-2133 A 20020708
CN 2003-819146 A3 20030707
WO 2003-SE1185 W 20030707

OTHER SOURCE(S): MARPAT 140:93937

GI



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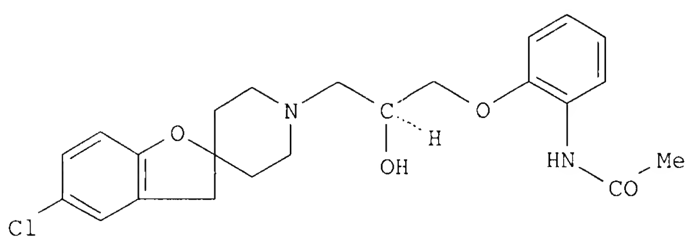


II

AB The invention provides tricyclic spiropiperidines or spiropyrrolidines (shown as I; variables defined below; e.g. II), processes for their preparation, pharmaceutical compns. containing them and their use in therapy for disorders affected by modulation of chemokine receptors (no data). For I: m is 0-4; each R1 = halogen, cyano, hydroxy, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy or sulfonamido; either X = a bond, -CH2-, -O- or -C(O)- and Y = a bond, -CH2-, -O- or -C(O)-, or X and Y together = -CH:CMe- or -CMe:CH-, and Z = a bond, -O-, -NH- or -CH2-, provided that only one of X,

Y and Z can be a bond at any one time and provided that X and Y do not both simultaneously = -O- or -C(O)-. N = 0-2; each R2 = halogen or C1-C6 alkyl; q = 0-1; R3 = -NHC(O)R10, -C(O)NR11R12 or -COOR12a; R4, R5, R6, R7 and R8 = H or a C1-C6 alkyl group; t = 0-2; each R9 = halogen, cyano, hydroxy, carboxy, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 haloalkyl, or C1-C6 alkyl; addnl. details are given in the claims. Methods of preparation are claimed and >200 example prepns. are included. For example, II was prepared in 2 steps starting from N-(2-hydroxyphenyl)acetamide, ((2S)-oxiran-2-yl)methyl and Cs2CO3 in DMF to give N-[2-[((2S)-oxiran-2-yl)methoxy]phenyl]acetamide as an intermediate, which was reacted with 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] in EtOH to give II.

IT 644969-62-0P 644969-63-1P

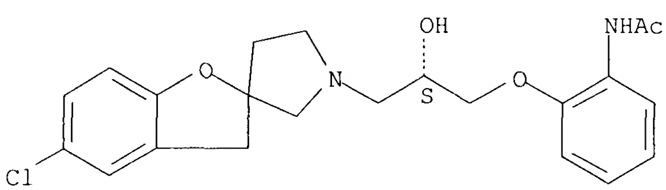
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(drug candidate, chiral resolution; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

RN 644969-62-0 CAPLUS

CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

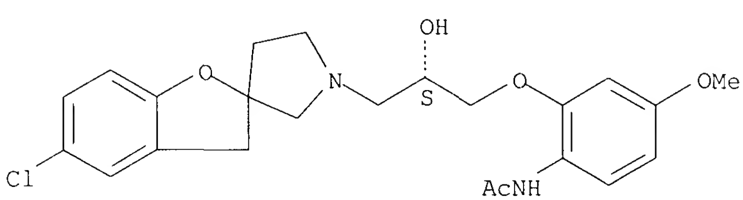
Absolute stereochemistry.



RN 644969-63-1 CAPLUS

CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



IT 644969-61-9P 644969-64-2P

RL: PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

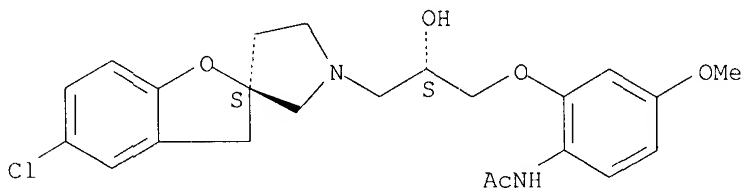
(drug candidate; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

RN 644969-61-9 CAPLUS

CN Acetamide, N-[2-[(2S)-3-[(2S)-5-chlorospiro[benzofuran-2(3H),3'-

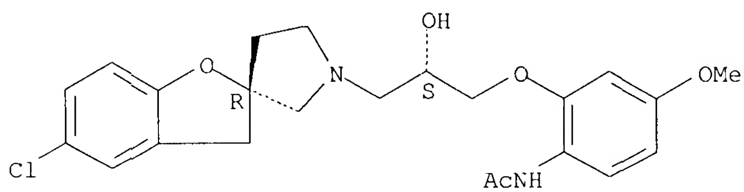
pyrrolidin]-1'-yl]-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



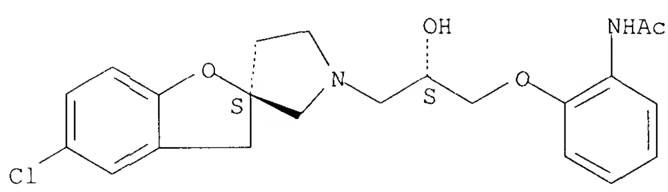
RN 644969-64-2 CAPLUS
CN Acetamide, N-[2-[(2S)-3-[(2R)-5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl]-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



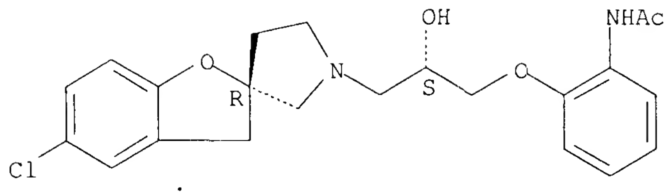
IT 644969-59-5P 644969-60-8P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)
RN 644969-59-5 CAPLUS
CN Acetamide, N-[2-[(2S)-3-[(2S)-5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl]-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644969-60-8 CAPLUS
CN Acetamide, N-[2-[(2S)-3-[(2R)-5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl]-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



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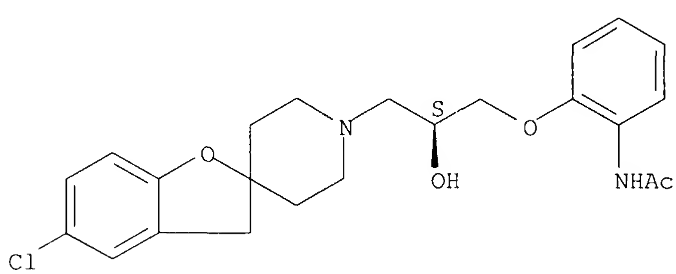
644971-52-8P 644971-55-1P 644971-61-9P
644972-78-1P 644972-80-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

RN 644968-64-9 CAPLUS

CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

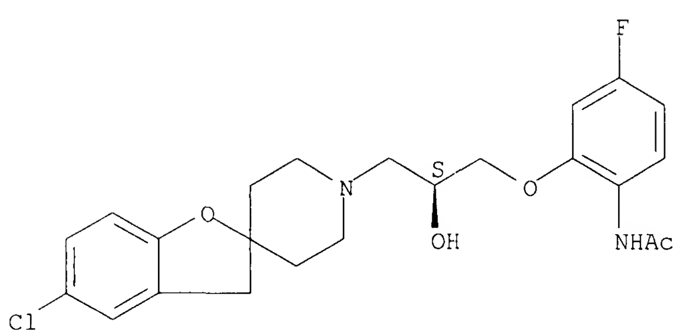
Absolute stereochemistry.



RN 644968-67-2 CAPLUS

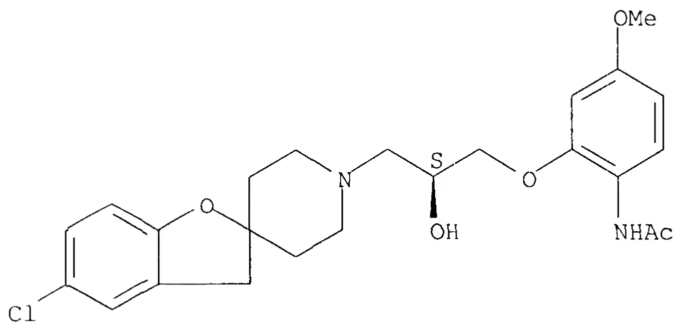
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluorophenyl]- (CA INDEX NAME)

Absolute stereochemistry.



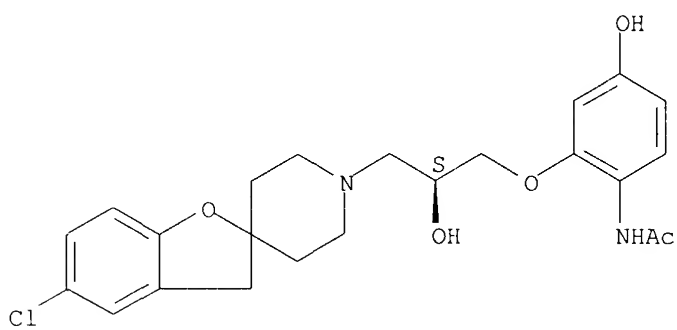
RN 644968-71-8 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



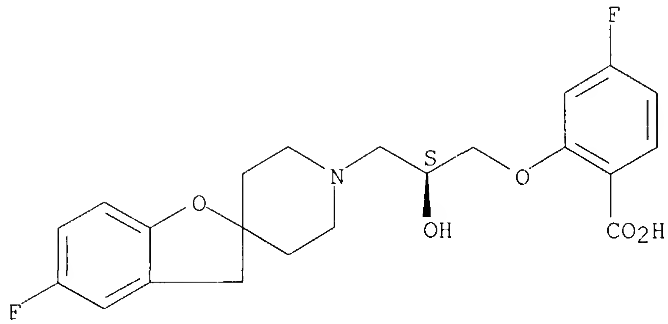
RN 644968-75-2 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



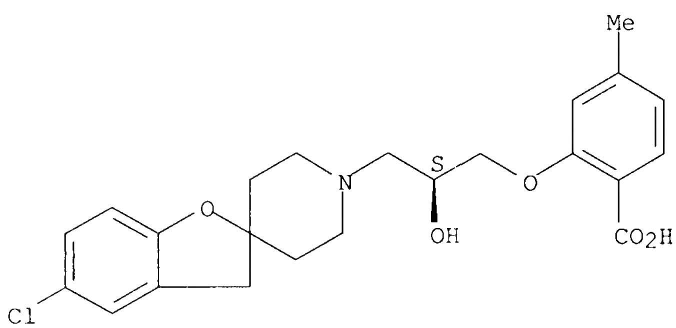
RN 644970-19-4 CAPLUS
CN Benzoic acid, 4-fluoro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



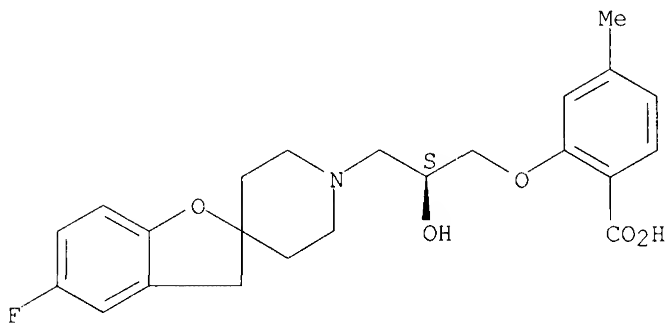
RN 644970-24-1 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methyl-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-28-5 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methyl-, hydrochloride (9CI) (CA INDEX NAME)

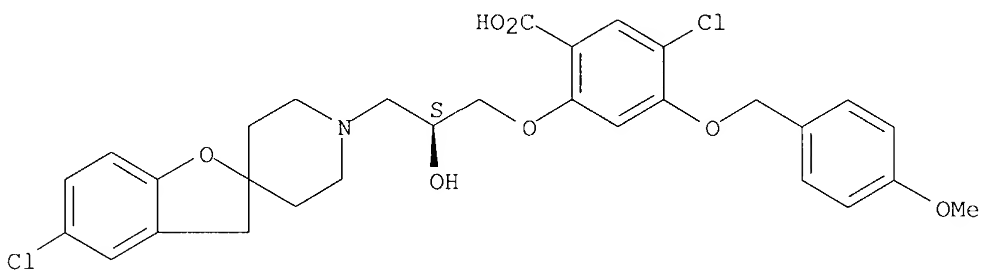
Absolute stereochemistry.



● HCl

RN 644971-09-5 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



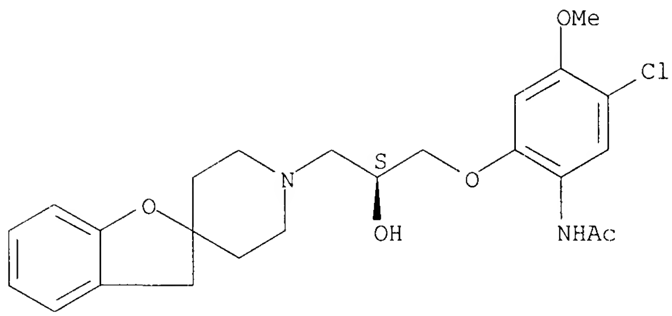
● HCl

RN 644971-31-3 CAPLUS
CN Acetamide, N-[5-chloro-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-4-methoxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

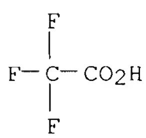
CRN 644971-30-2
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

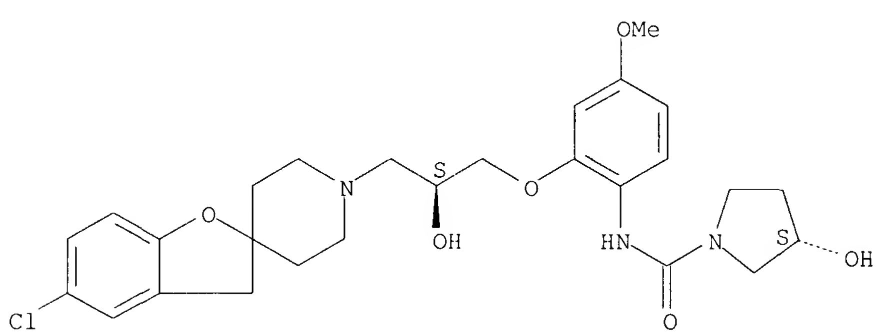


RN 644971-35-7 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]-3-hydroxy-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

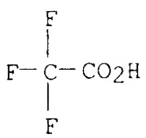
CRN 644971-34-6
CMF C27 H34 Cl N3 O6

Absolute stereochemistry.



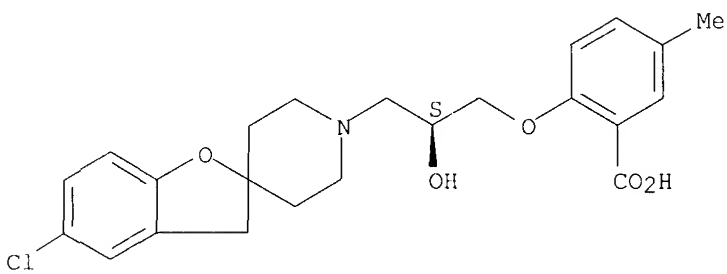
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644971-43-7 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-methyl-, hydrochloride (9CI) (CA INDEX NAME)

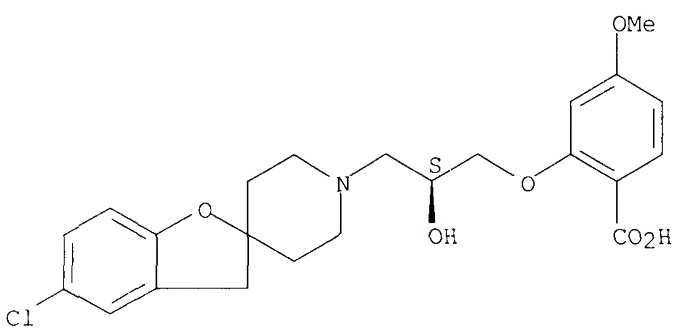
Absolute stereochemistry.



● HCl

RN 644971-47-1 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxy-, hydrochloride (9CI) (CA INDEX NAME)

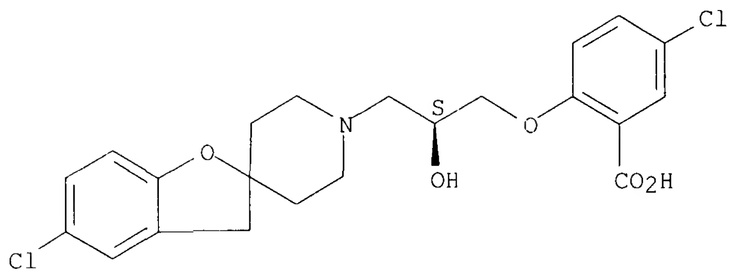
Absolute stereochemistry.



● HCl

RN 644971-52-8 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, hydrochloride (9CI) (CA INDEX NAME)

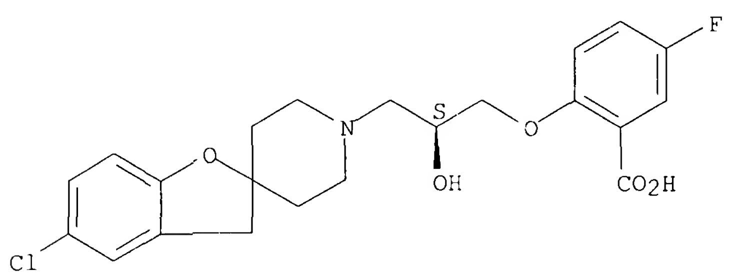
Absolute stereochemistry.



● HCl

RN 644971-55-1 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-fluoro-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



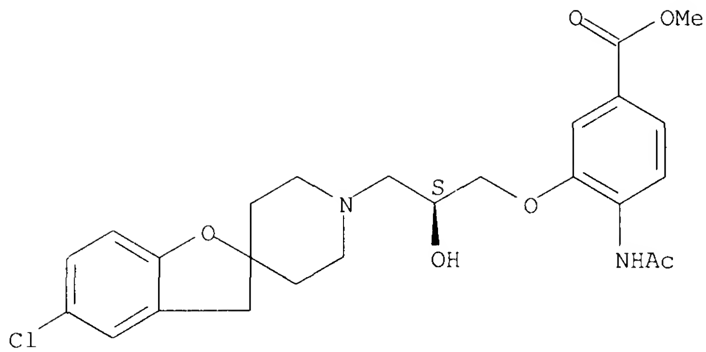
● HCl

RN 644971-61-9 CAPLUS
CN Benzoic acid, 4-(acetylamino)-3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, methyl ester, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

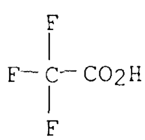
CRN 644971-60-8
CMF C25 H29 Cl N2 O6

Absolute stereochemistry.



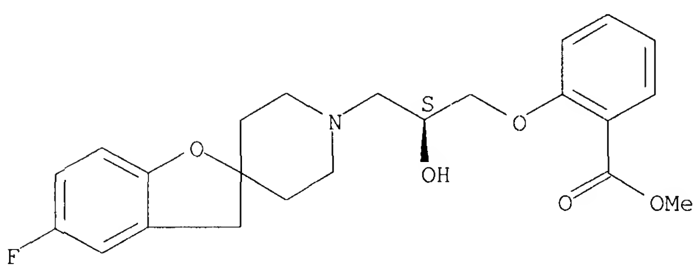
CM 2

CRN 76-05-1
CMF C2 H F3 O2



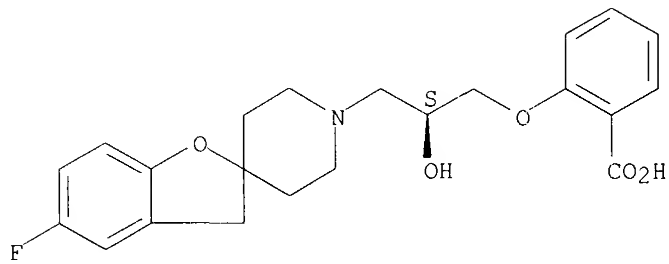
RN 644972-78-1 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 644972-80-5 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

IT 644968-77-4P 644968-79-6P 644968-80-9P
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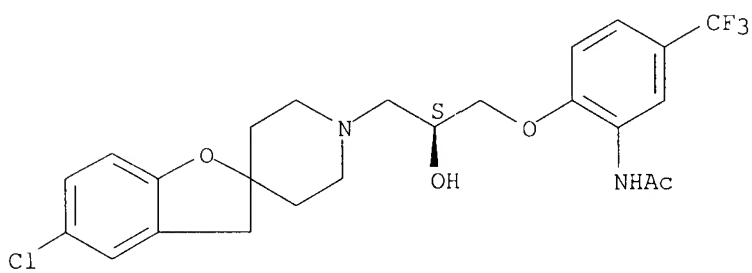
645389-76-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

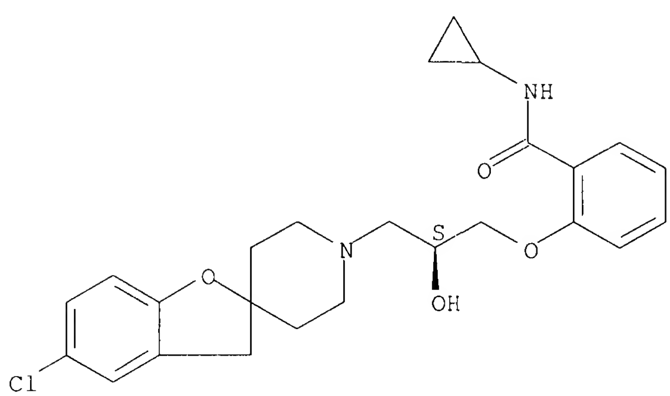
RN 644968-77-4 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-(trifluoromethyl)phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



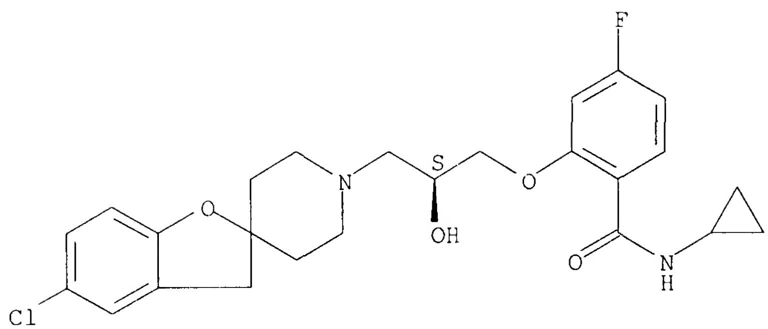
RN 644968-79-6 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-cyclopropyl- (CA INDEX NAME)

Absolute stereochemistry.



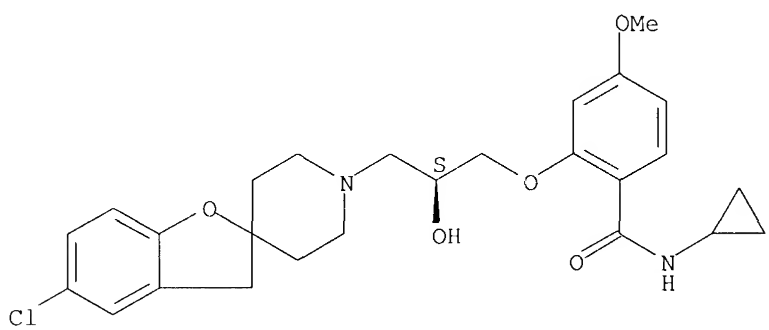
RN 644968-80-9 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-cyclopropyl-4-fluoro- (CA INDEX NAME)

Absolute stereochemistry.



RN 644968-83-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-cyclopropyl-4-methoxy- (CA INDEX NAME)

Absolute stereochemistry.

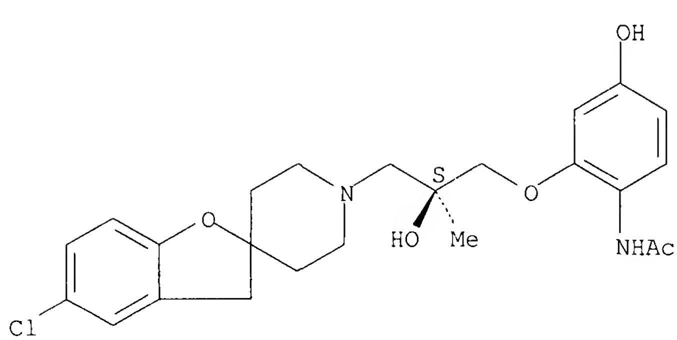


RN 644968-87-6 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

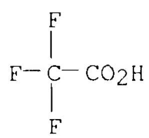
CRN 644968-86-5
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



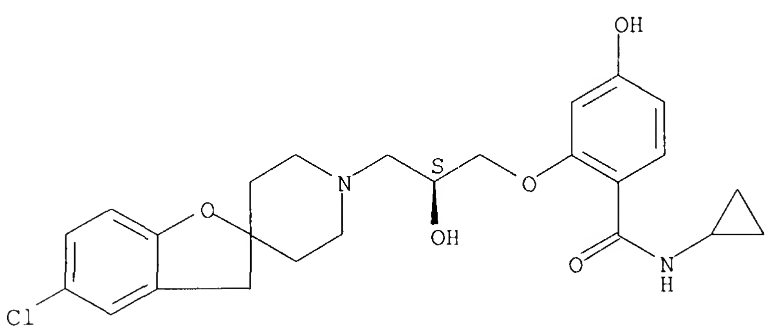
CM 2

CRN 76-05-1
CMF C2 H F3 O2



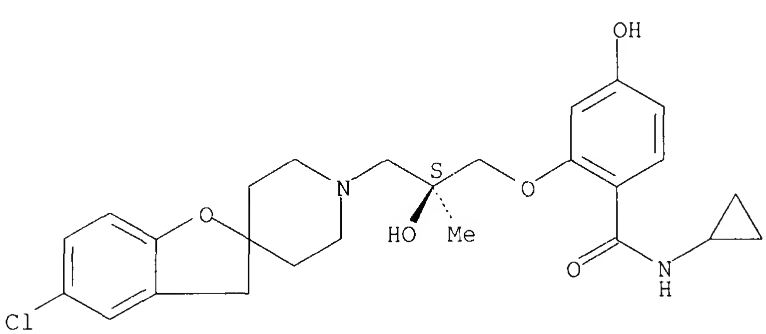
RN 644969-08-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-cyclopropyl-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



RN 644969-11-9 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-N-cyclopropyl-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

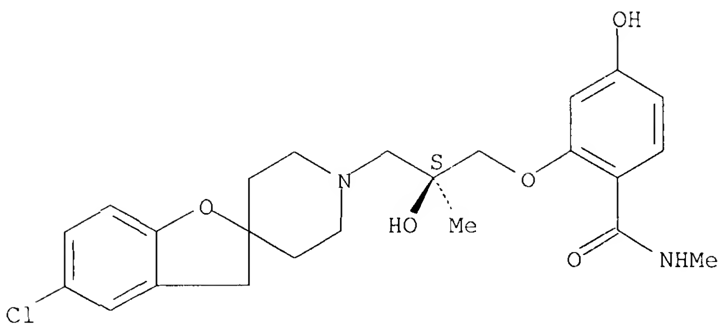


RN 644969-20-0 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-4-hydroxy-N-methyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

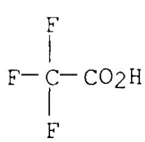
CRN 644969-19-7
CMF C24 H29 Cl N2 O5

Absolute stereochemistry.



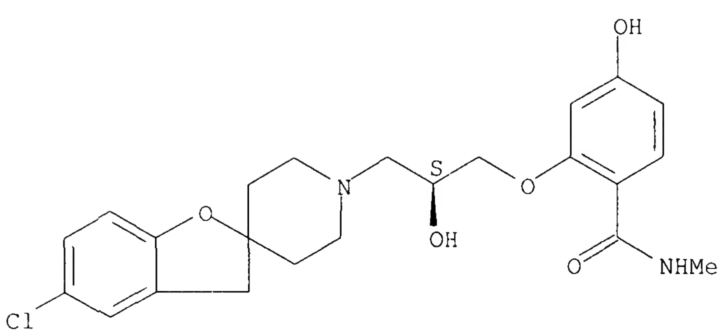
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644969-24-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

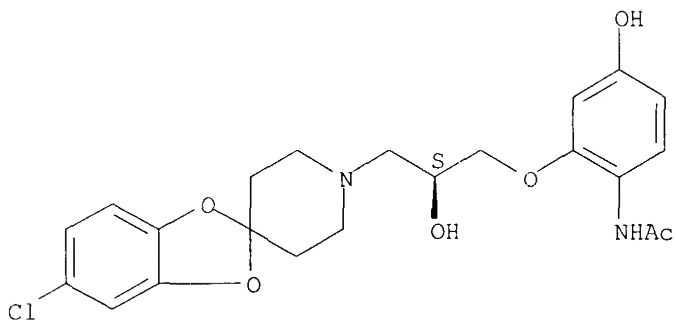


RN 644969-28-8 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

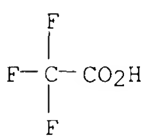
CRN 644969-27-7
CMF C22 H25 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

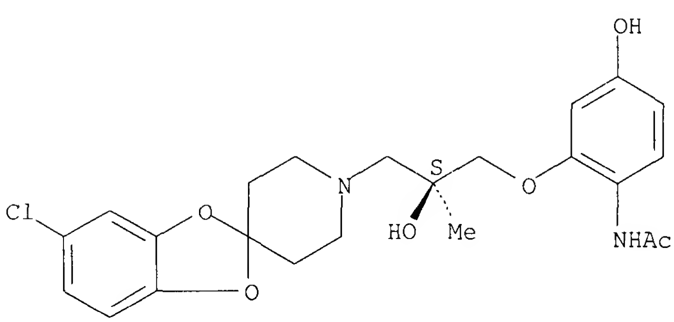


RN 644969-31-3 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chlorospiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

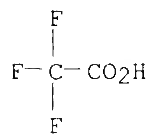
CRN 644969-30-2
CMF C23 H27 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

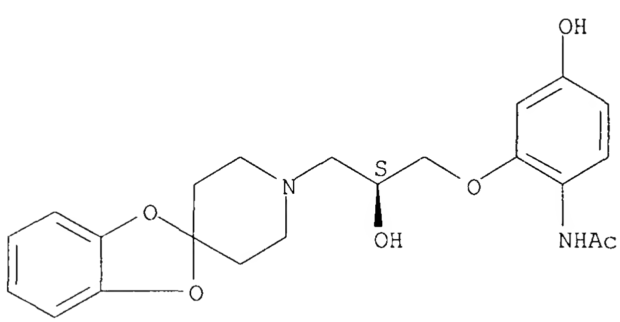


RN 644969-34-6 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-ylpropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

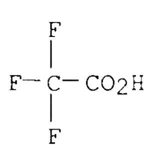
CRN 644969-33-5
CMF C22 H26 N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

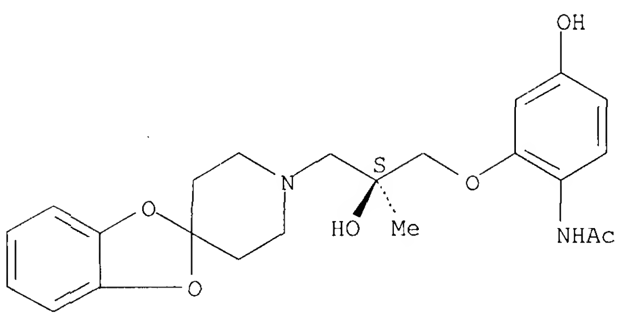


RN 644969-36-8 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-2-methyl-3-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-ylpropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

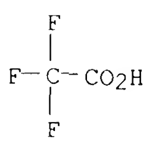
CRN 644969-35-7
CMF C23 H28 N2 O6

Absolute stereochemistry.



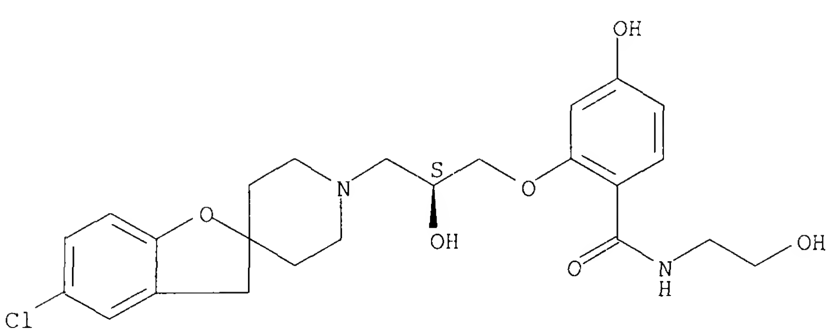
CM 2

CRN 76-05-1
CMF C2 H F3 O2



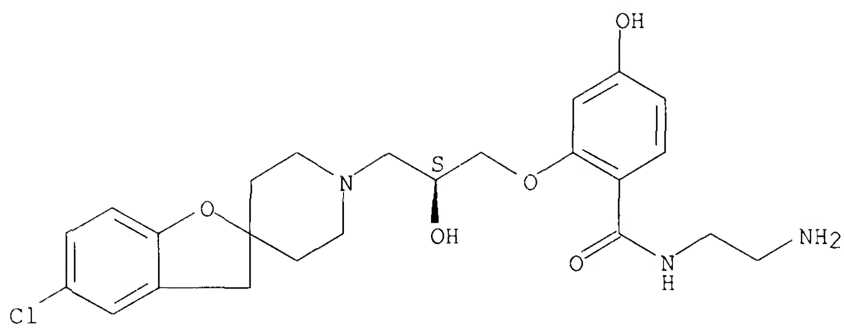
RN 644969-48-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxyethyl)- (CA INDEX NAME)

Absolute stereochemistry.



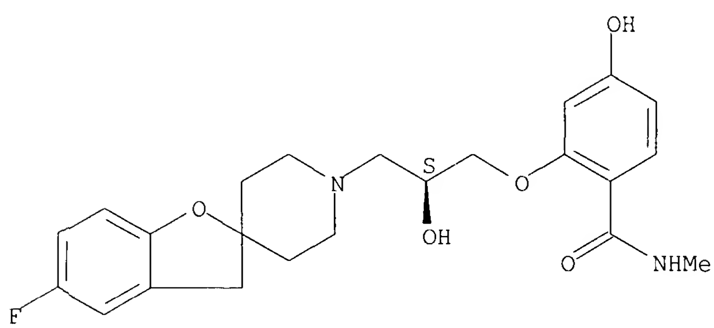
RN 644969-52-8 CAPLUS
CN Benzamide, N-(2-aminoethyl)-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



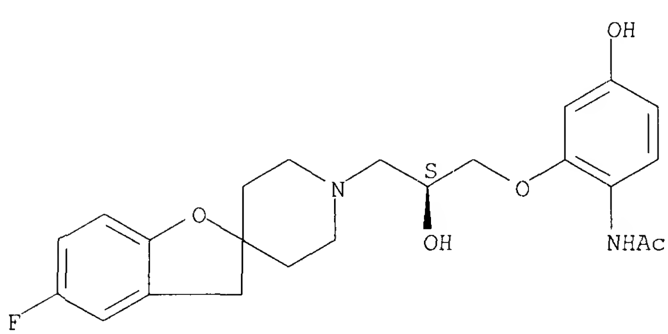
RN 644969-55-1 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



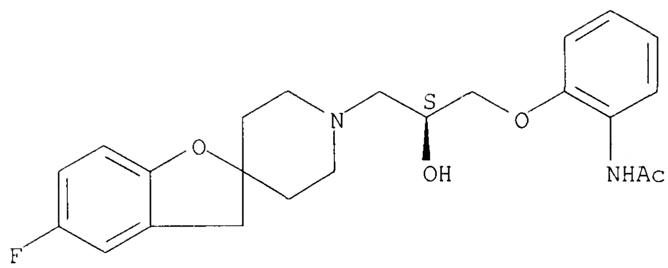
RN 644969-57-3 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



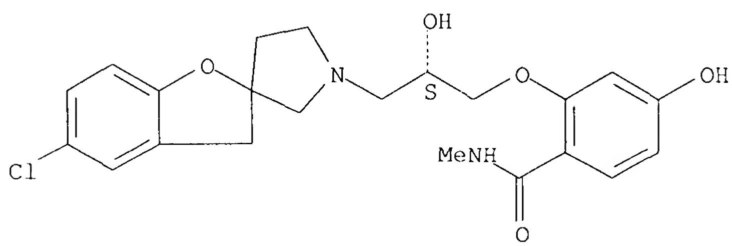
RN 644969-58-4 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644969-65-3 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

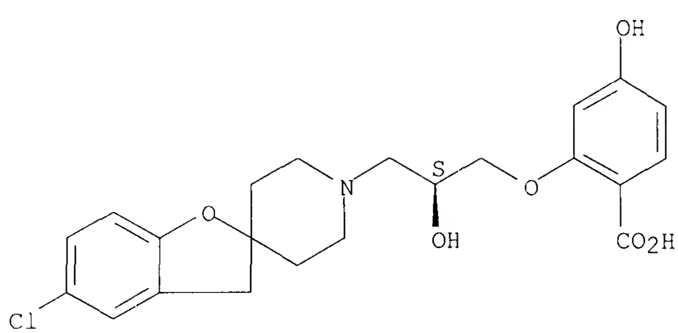


RN 644969-67-5 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 644969-54-0
CMF C22 H24 Cl N O6

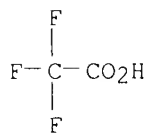
Absolute stereochemistry.



CM 2

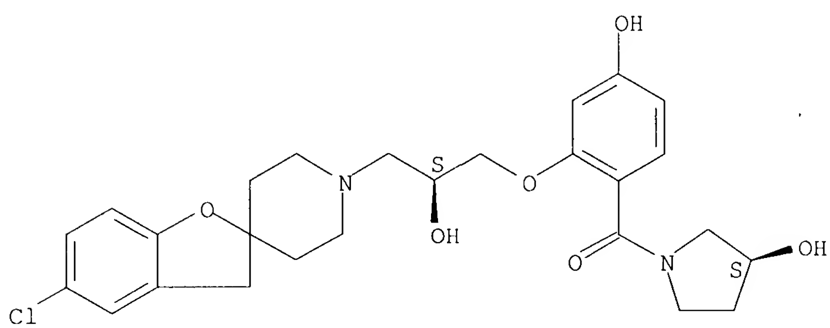
CRN 76-05-1

CMF C2 H F3 O2



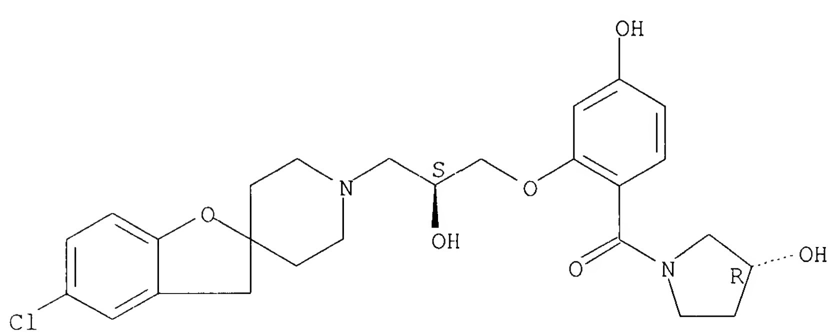
RN 644969-69-7 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



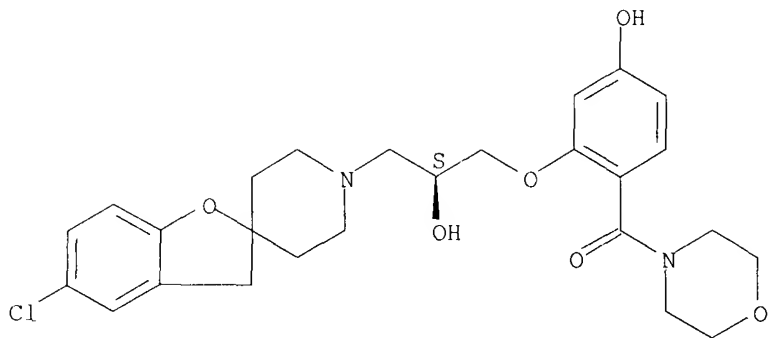
RN 644969-71-1 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644969-73-3 CAPLUS
CN Morpholine, 4-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644969-76-6 CAPLUS

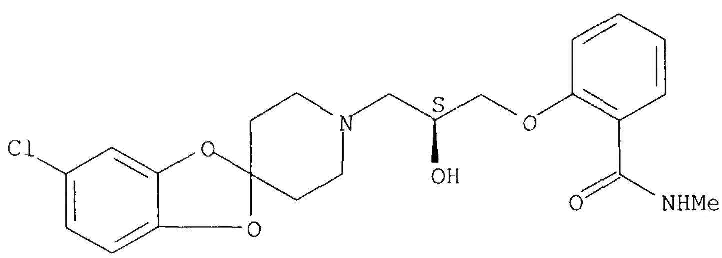
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-methyl-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 644969-75-5

CMF C22 H25 Cl N2 O5

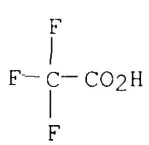
Absolute stereochemistry.



CM 2

CRN 76-05-1

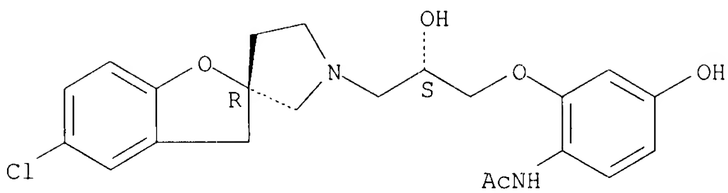
CMF C2 H F3 O2



RN 644969-88-0 CAPLUS

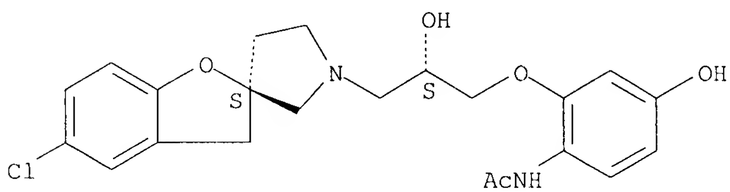
CN Acetamide, N-[2-[(2S)-3-[(2R)-5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl]-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



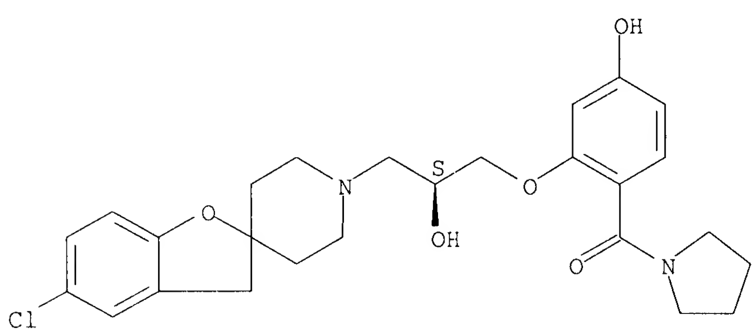
RN 644969-89-1 CAPLUS
CN Acetamide, N-[2-[(2S)-3-[(2S)-5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl]-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



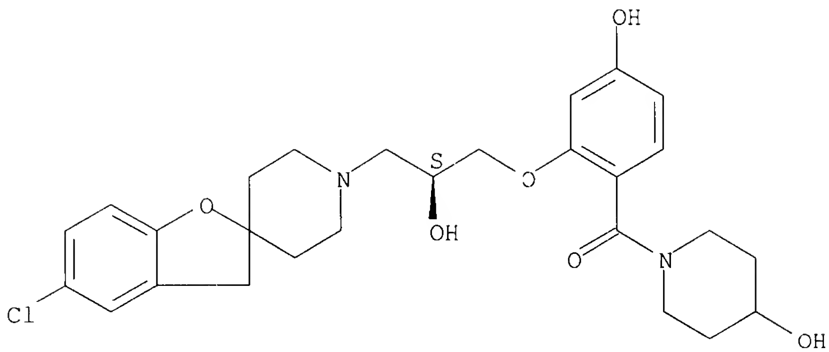
RN 644969-90-4 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



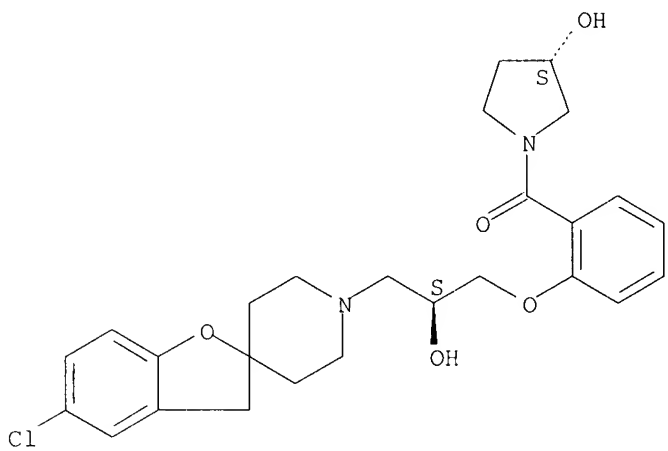
RN 644969-93-7 CAPLUS
CN 4-Piperidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



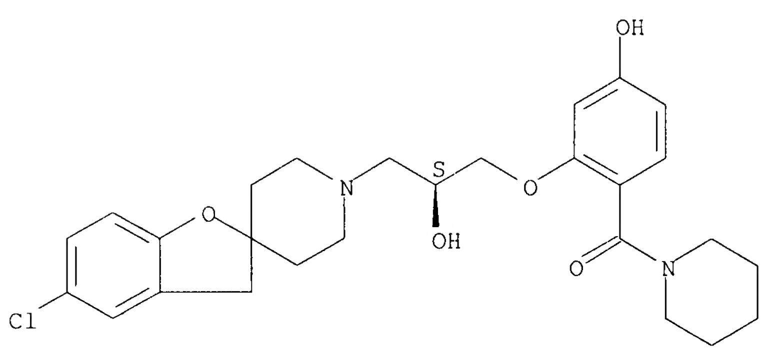
RN 644969-95-9 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



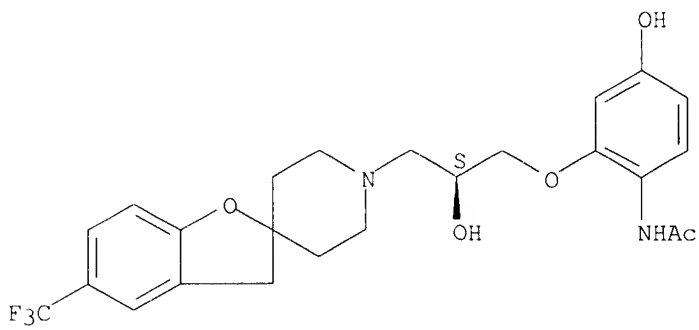
RN 644969-96-0 CAPLUS
CN Piperidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



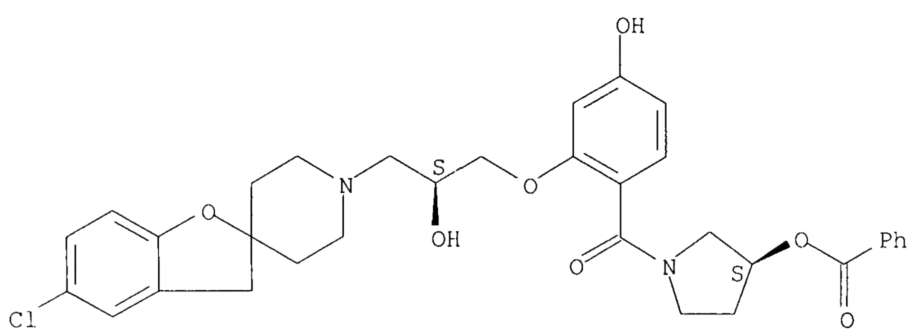
RN 644970-04-7 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-[5-(trifluoromethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]propoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



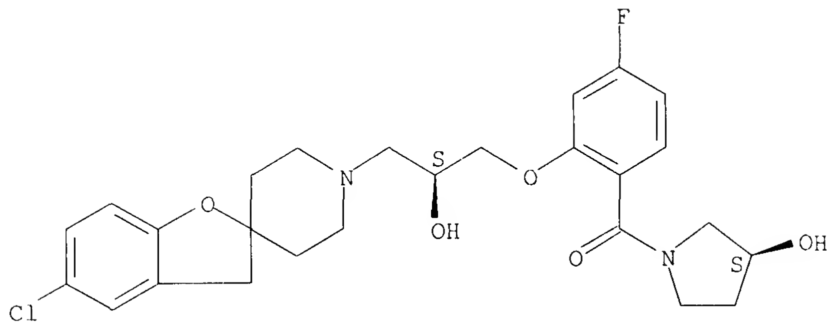
RN 644970-05-8 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, benzoate (ester), (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



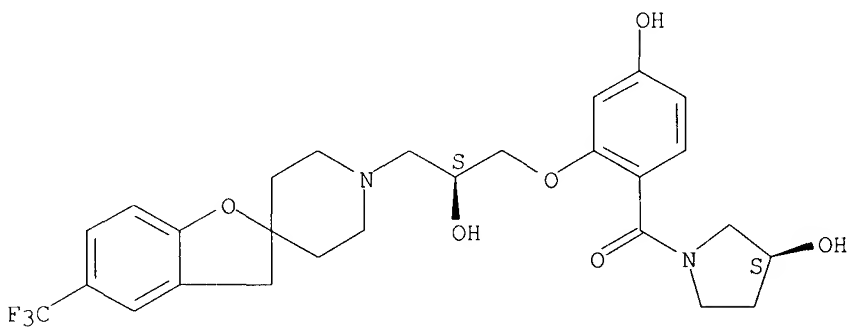
RN 644970-08-1 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluorobenzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



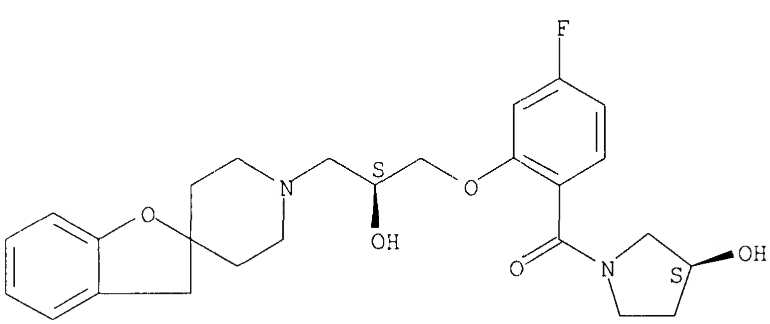
RN 644970-12-7 CAPLUS
CN 3-Pyrrolidinol, 1-[4-hydroxy-2-[(2S)-2-hydroxy-3-[5-(trifluoromethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]propoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



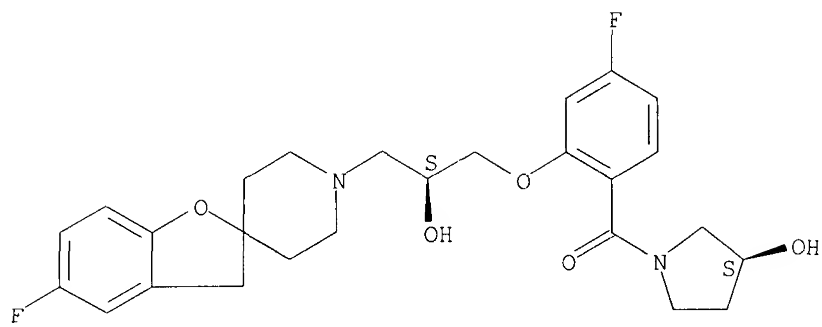
RN 644970-16-1 CAPLUS
CN 3-Pyrrolidinol, 1-[4-fluoro-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



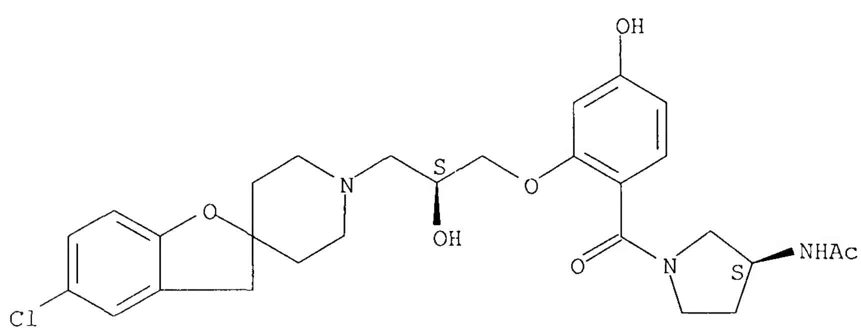
RN 644970-21-8 CAPLUS
CN 3-Pyrrolidinol, 1-[4-fluoro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



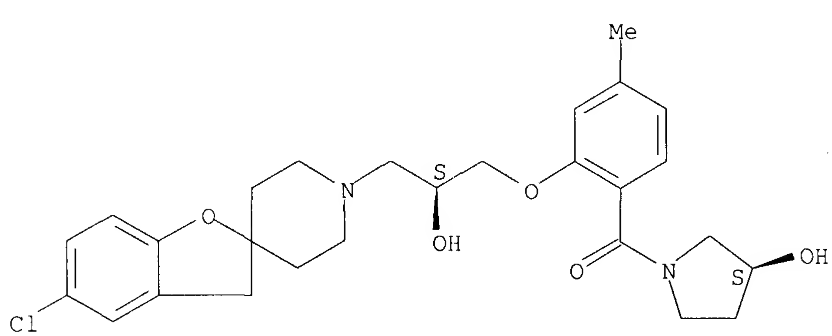
RN 644970-22-9 CAPLUS
CN Acetamide, N-[(3S)-1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-3-pyrrolidinyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-27-4 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methylbenzoyl]-, (3S)- (9CI) (CA INDEX NAME)

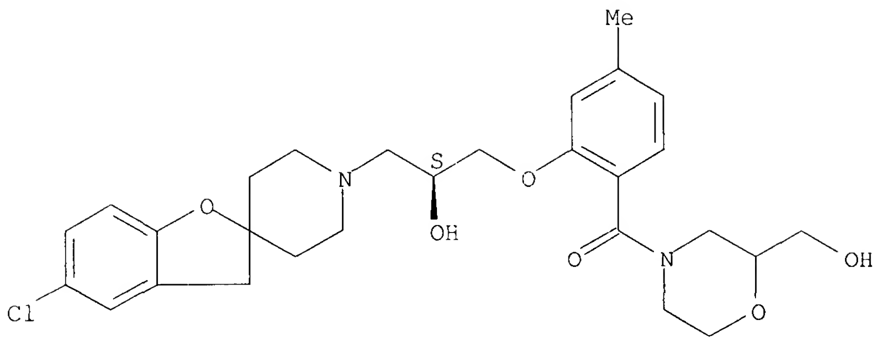
Absolute stereochemistry.



RN 644970-30-9 CAPLUS
CN 2-Morpholinemethanol, 4-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methylbenzoyl]- (9CI) (CA INDEX

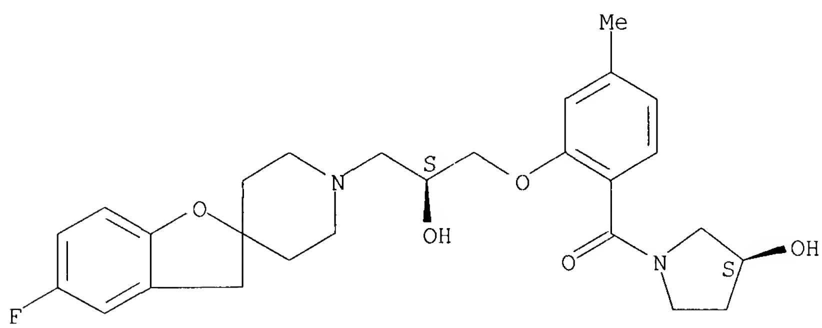
NAME)

Absolute stereochemistry.



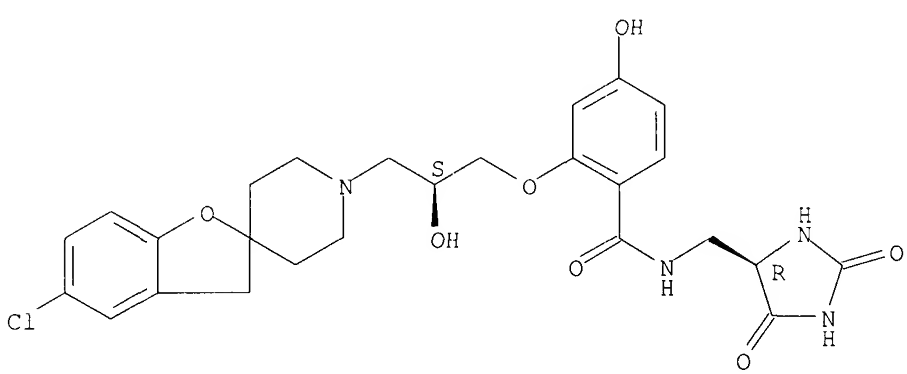
RN 644970-31-0 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methylbenzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



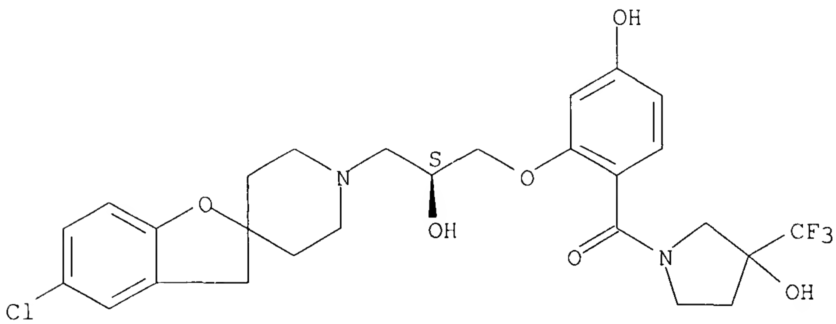
RN 644970-32-1 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-[[(4R)-2,5-dioxo-4-imidazolidinyl]methyl]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



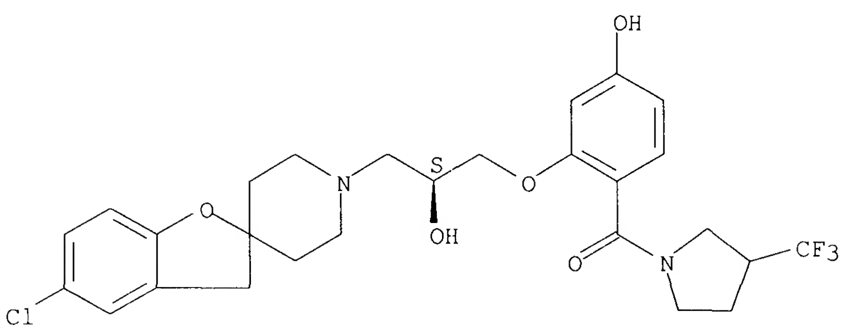
RN 644970-35-4 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



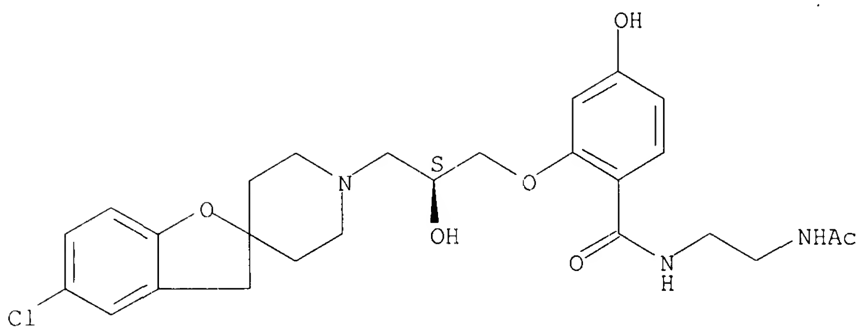
RN 644970-39-8 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



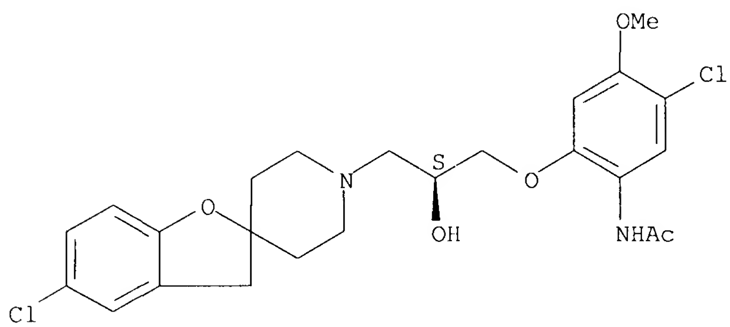
RN 644970-44-5 CAPLUS
CN Benzamide, N-[2-(acetylamino)ethyl]-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-46-7 CAPLUS
CN Acetamide, N-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.

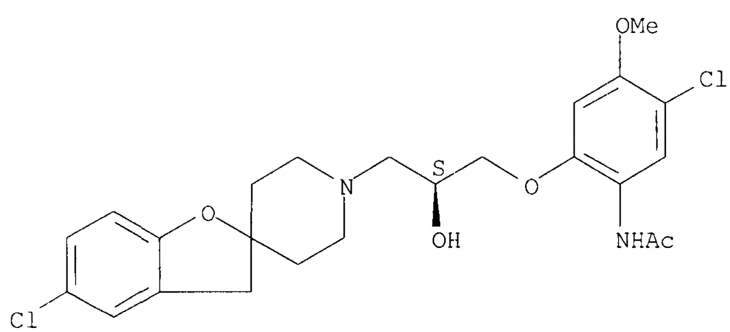


RN 644970-47-8 CAPLUS
CN Acetamide, N-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

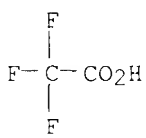
CRN 644970-46-7
CMF C24 H28 Cl2 N2 O5

Absolute stereochemistry.



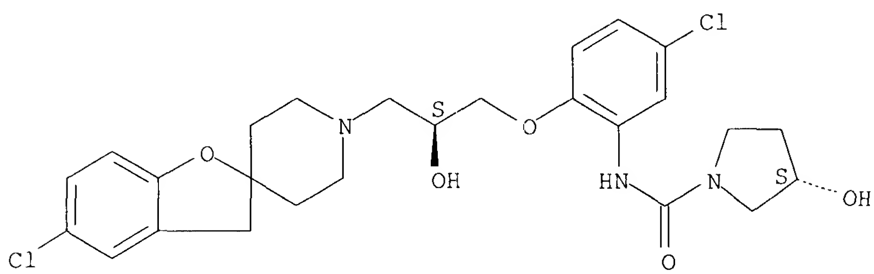
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644970-49-0 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-3-hydroxy-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

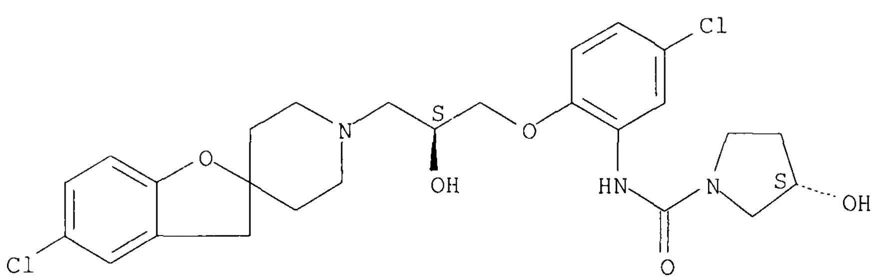


RN 644970-50-3 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-3-hydroxy-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

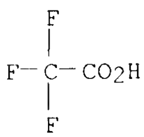
CRN 644970-49-0
CMF C26 H31 Cl2 N3 O5

Absolute stereochemistry.



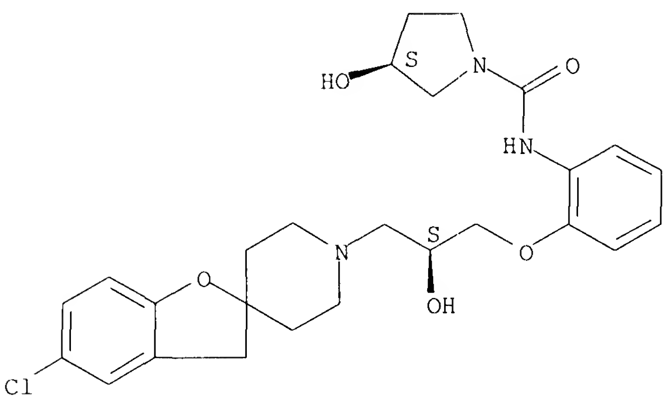
CM 2

CRN 76-05-1
CMF C2 H F3 O2



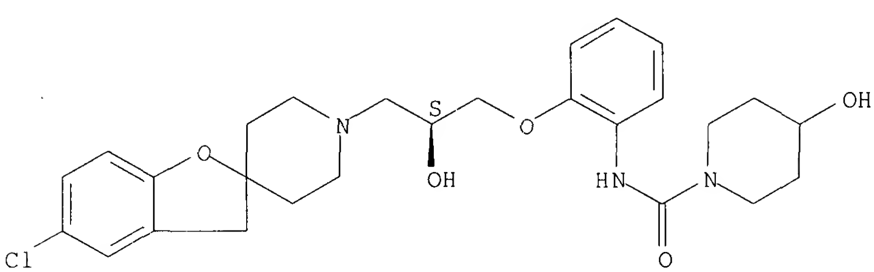
RN 644970-53-6 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-3-hydroxy-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-54-7 CAPLUS
CN 1-Piperidinecarboxamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

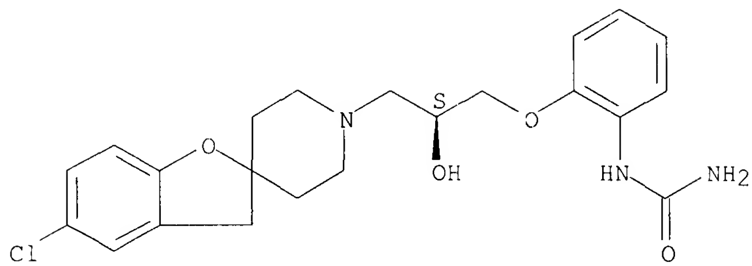


RN 644970-56-9 CAPLUS
CN Urea, [2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

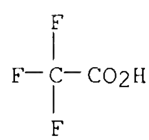
CRN 644970-55-8
CMF C22 H26 Cl N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

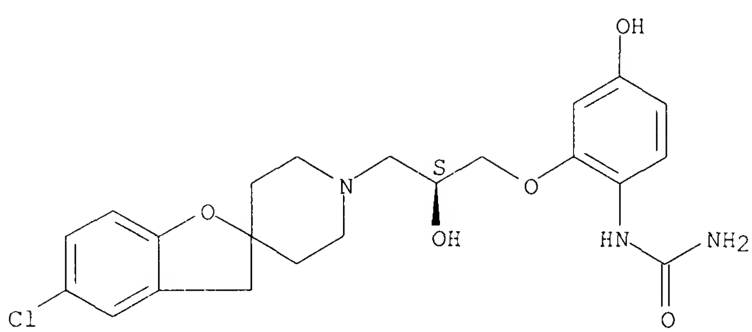


RN 644970-59-2 CAPLUS
CN Urea, [2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

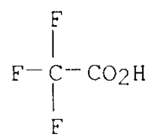
CRN 644970-58-1
CMF C22 H26 Cl N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

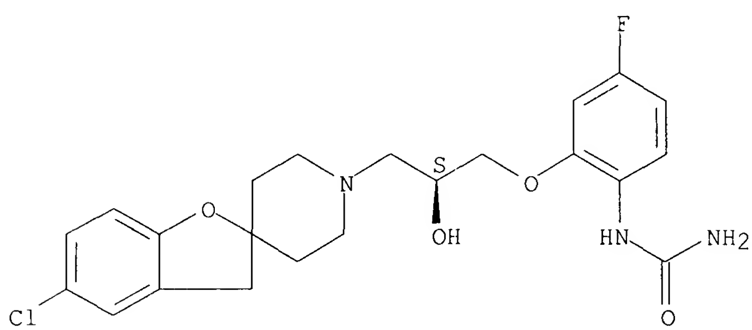


RN 644970-63-8 CAPLUS
CN Urea, [2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluorophenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

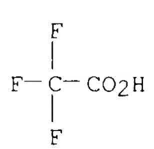
CRN 644970-62-7
CMF C22 H25 Cl F N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

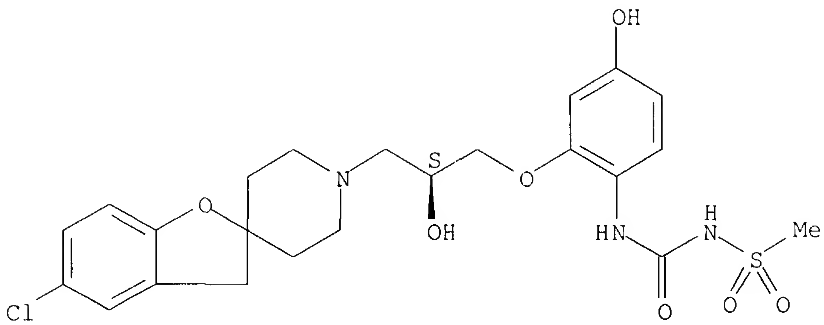


RN 644970-66-1 CAPLUS
CN Methanesulfonamide, N-[[[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]amino]carbonyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

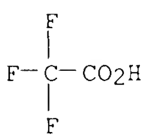
CRN 644970-65-0
CMF C23 H28 Cl N3 O7 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

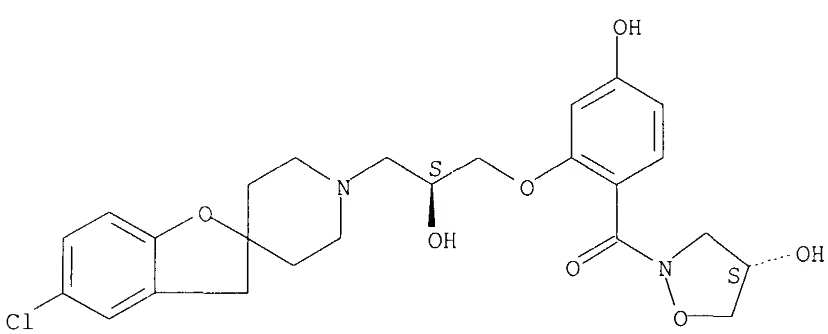


RN 644970-68-3 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (4S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

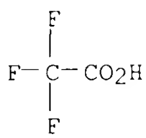
CRN 644970-67-2
CMF C25 H29 Cl N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

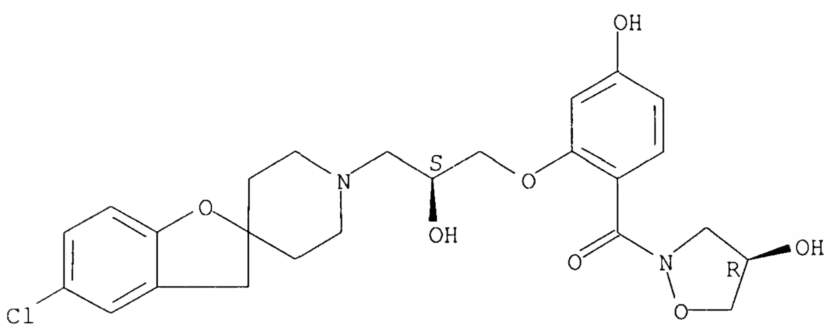


RN 644970-72-9 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (4R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

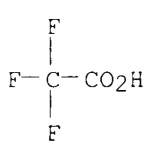
CRN 644970-71-8
CMF C25 H29 Cl N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

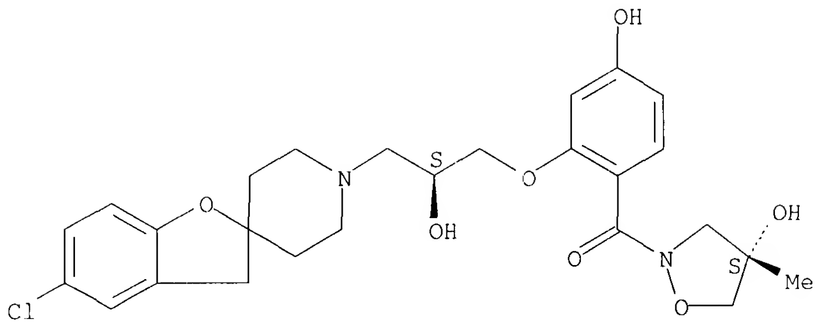


RN 644970-75-2 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-methyl-, (4S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

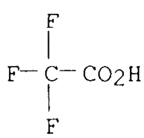
CRN 644970-74-1
CMF C26 H31 Cl N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

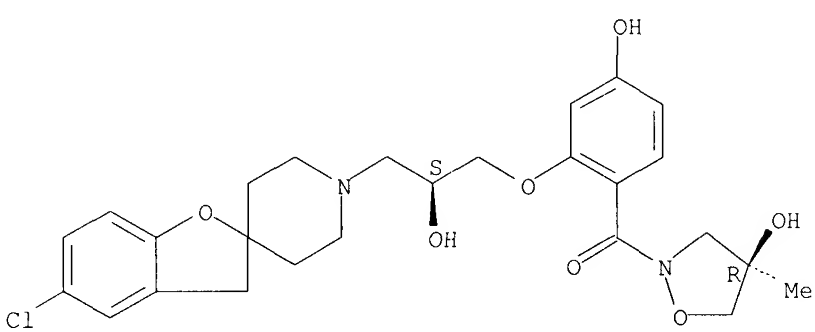


RN 644970-82-1 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-methyl-, (4R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

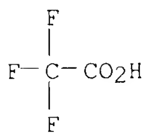
CRN 644970-81-0
CMF C26 H31 Cl N2 O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

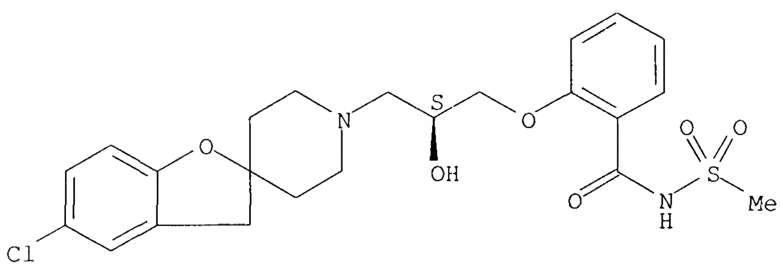


RN 644970-88-7 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(methylsulfonyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

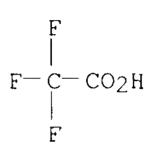
CRN 644970-87-6
CMF C23 H27 Cl N2 O6 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

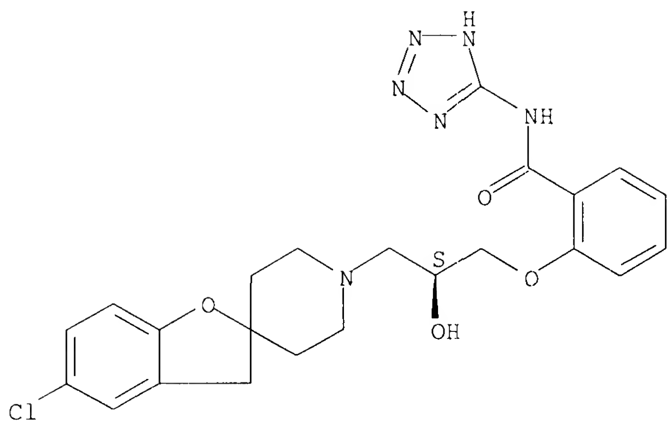


RN 644970-94-5 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-1H-tetrazol-5-yl-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

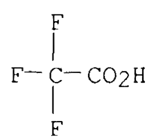
CRN 644970-93-4
CMF C23 H25 Cl N6 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

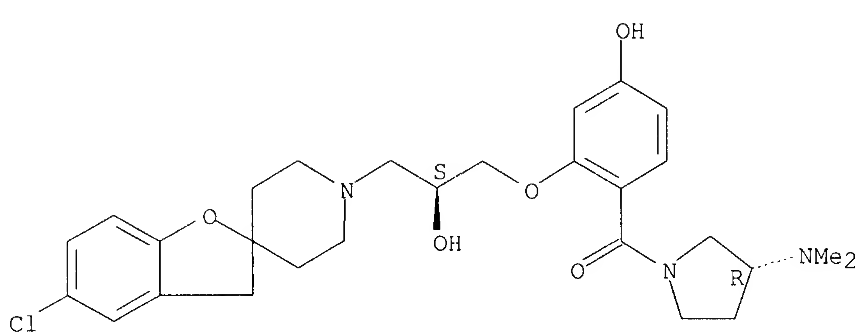


RN 644970-99-0 CAPLUS
CN 3-Pyrrolidinamine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-N,N-dimethyl-, (3R)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

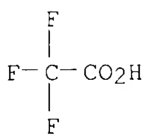
CRN 644970-98-9
CMF C28 H36 Cl N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

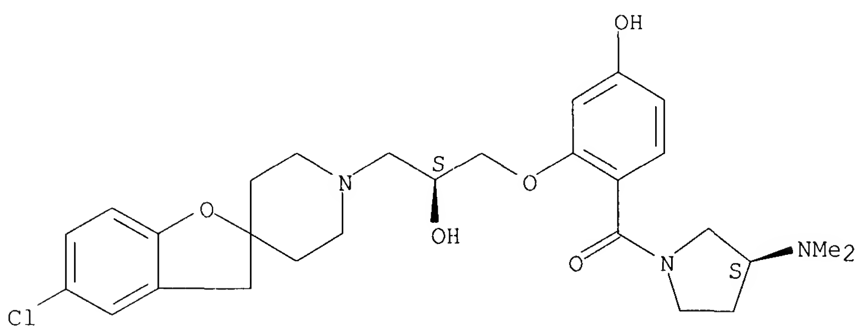


RN 644971-01-7 CAPLUS
CN 3-Pyrrolidinamine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-N,N-dimethyl-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

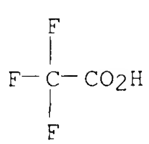
CRN 644971-00-6
CMF C28 H36 Cl N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



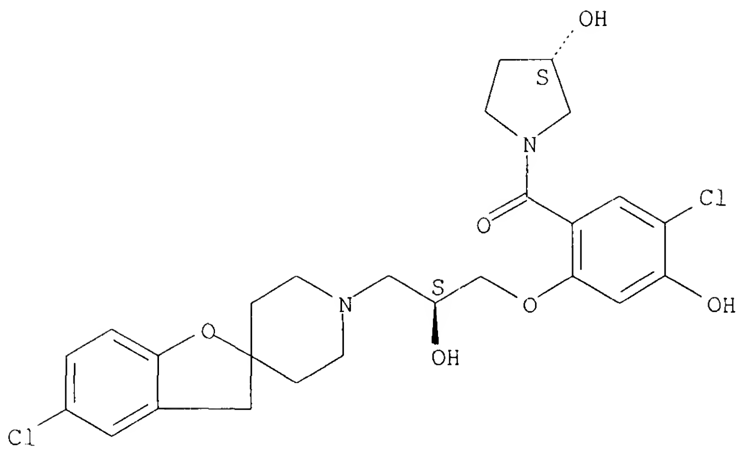
RN 644971-04-0 CAPLUS
CN 3-Pyrrolidinol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 644971-03-9

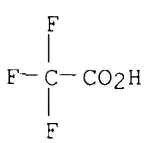
CMF C26 H30 Cl2 N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

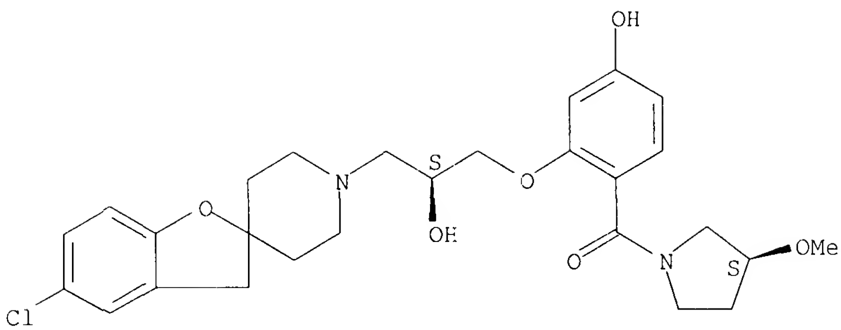


RN 644971-13-1 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-3-methoxy-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

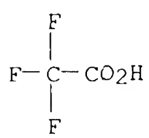
CRN 644971-12-0
CMF C27 H33 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

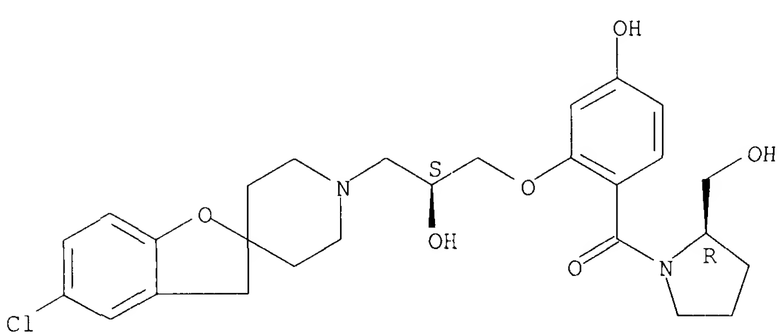


RN 644971-16-4 CAPLUS
CN 2-Pyrrolidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (2R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

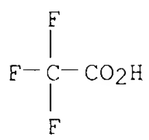
CRN 644971-15-3
CMF C27 H33 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

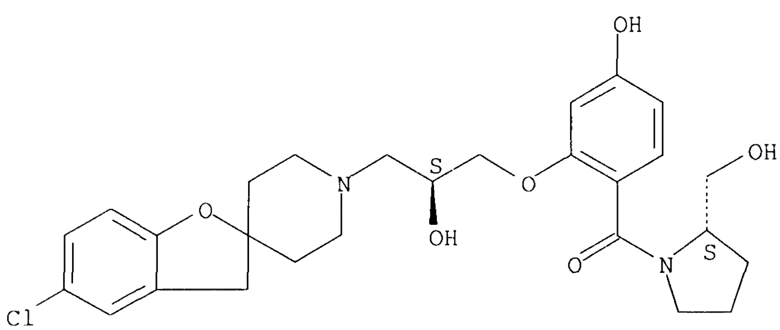


RN 644971-19-7 CAPLUS
CN 2-Pyrrolidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (2S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

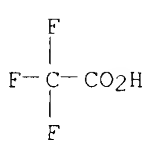
CRN 644971-18-6
CMF C27 H33 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

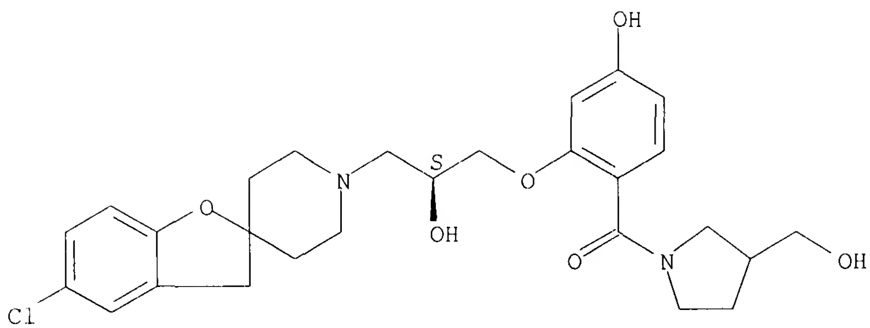


RN 644971-21-1 CAPLUS
CN 3-Pyrrolidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

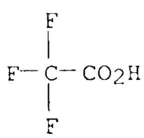
CRN 644971-20-0
CMF C27 H33 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

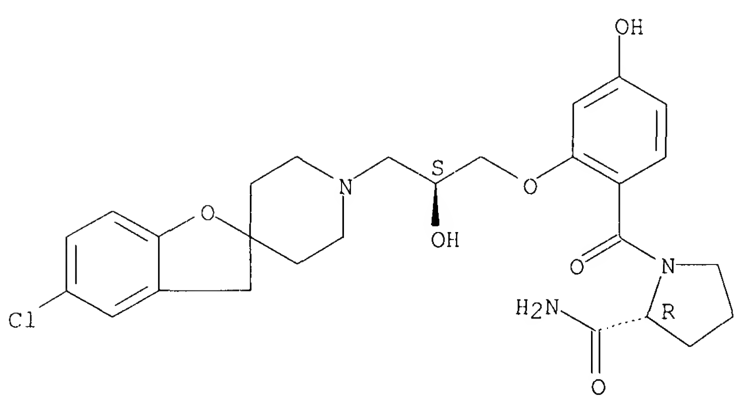


RN 644971-24-4 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (2R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

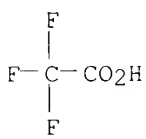
CRN 644971-23-3
CMF C27 H32 Cl N3 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

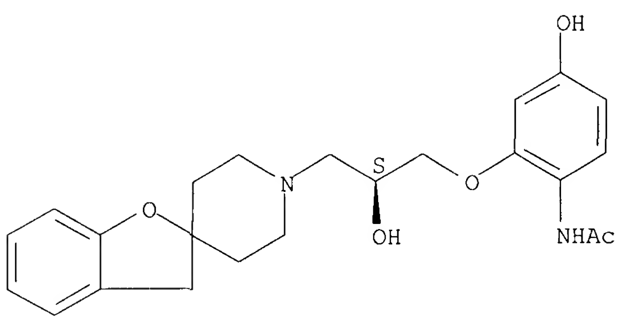


RN 644971-27-7 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

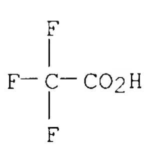
CRN 644971-26-6
CMF C23 H28 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

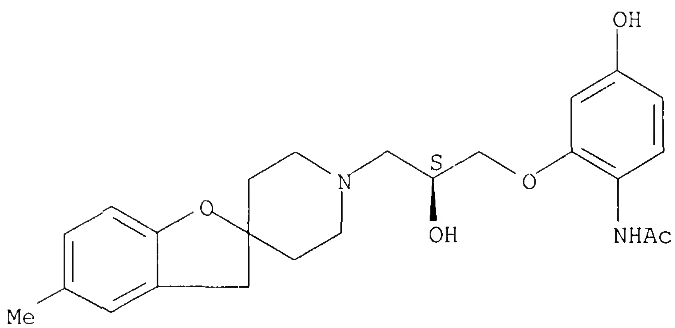


RN 644971-29-9 CAPLUS
CN Acetamide, N-[4-hydroxy-2-[(2S)-2-hydroxy-3-(5-methylspiro[benzofuran-2(3H),4'-piperidin]-1'-yl)propoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

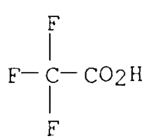
CRN 644971-28-8
CMF C24 H30 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

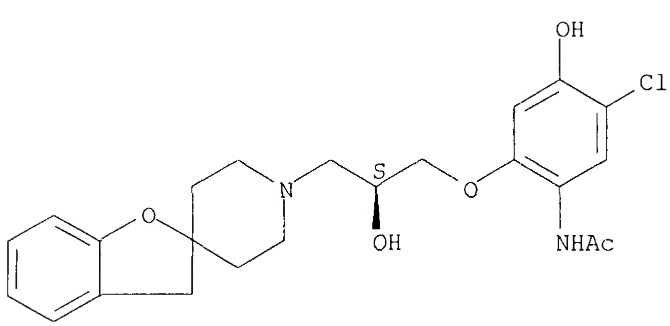


RN 644971-33-5 CAPLUS
CN Acetamide, N-[5-chloro-4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

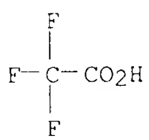
CRN 644971-32-4
CMF C23 H27 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

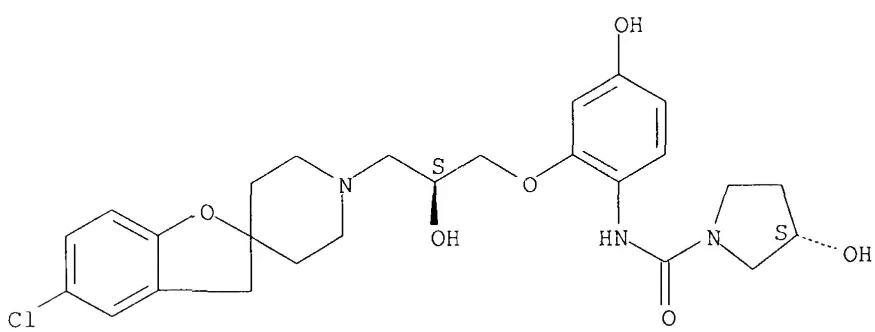


RN 644971-37-9 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-3-hydroxy-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

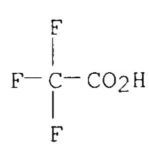
CRN 644971-36-8
CMF C26 H32 Cl N3 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

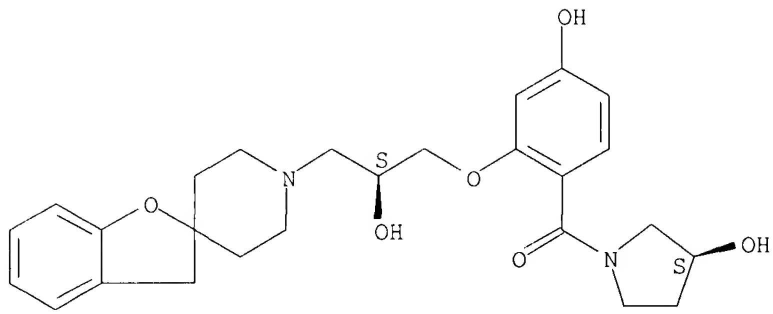


RN 644971-39-1 CAPLUS
CN 3-Pyrrolidinol, 1-[4-hydroxy-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]benzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

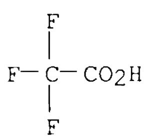
CRN 644971-38-0
CMF C26 H32 N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

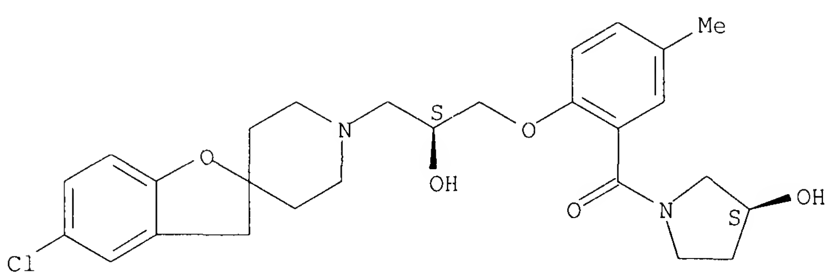


RN 644971-49-3 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-methylbenzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

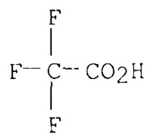
CRN 644971-48-2
CMF C27 H33 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

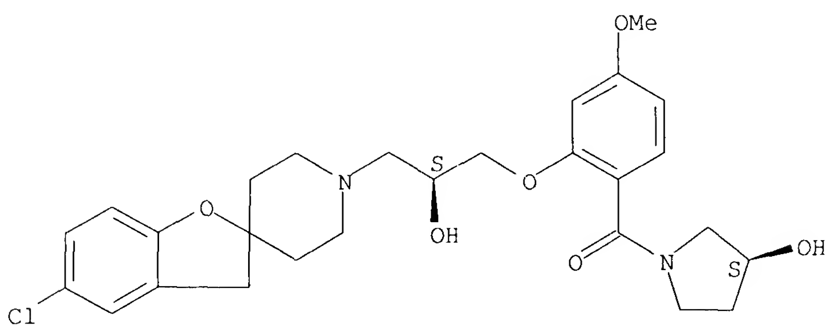


RN 644971-51-7 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxybenzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

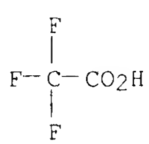
CRN 644971-50-6
CMF C27 H33 Cl N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

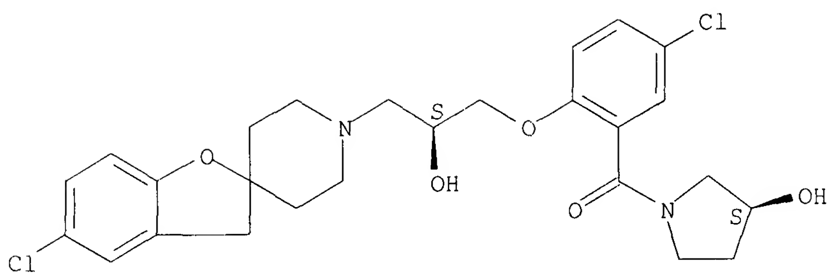


RN 644971-54-0 CAPLUS
CN 3-Pyrrolidinol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]benzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

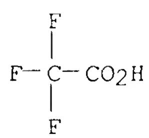
CRN 644971-53-9
CMF C26 H30 Cl2 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

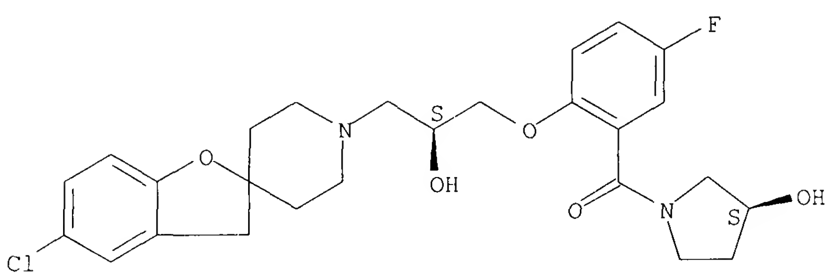


RN 644971-57-3 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-fluorobenzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

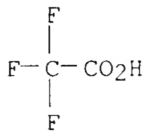
CRN 644971-56-2
CMF C26 H30 Cl F N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

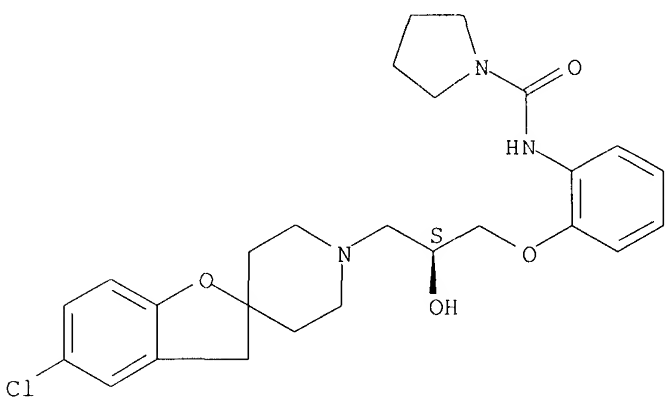


RN 644971-59-5 CAPLUS
CN 1-Pyrrolidinecarboxamide, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

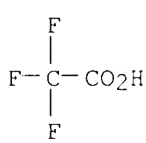
CRN 644971-58-4
CMF C26 H32 Cl N3 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

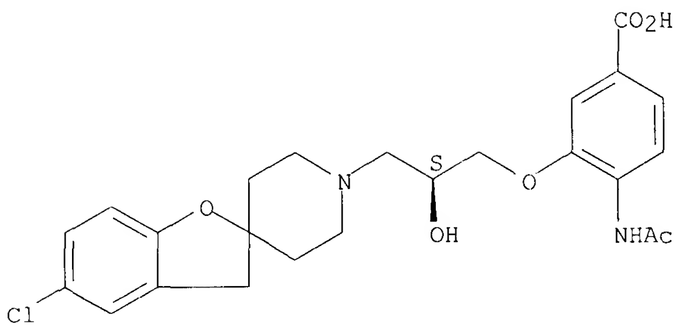


RN 644971-64-2 CAPLUS
CN Benzoic acid, 4-(acetylamino)-3-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

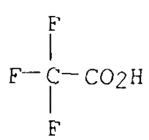
CRN 644971-63-1
CMF C24 H27 Cl N2 O6

Absolute stereochemistry.



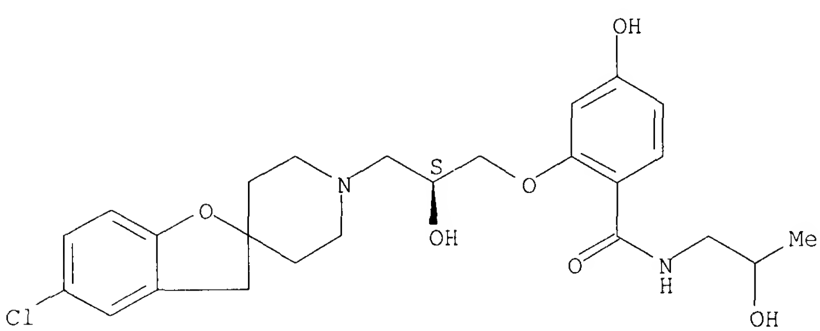
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644971-65-3 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxypropyl)- (CA INDEX NAME)

Absolute stereochemistry.

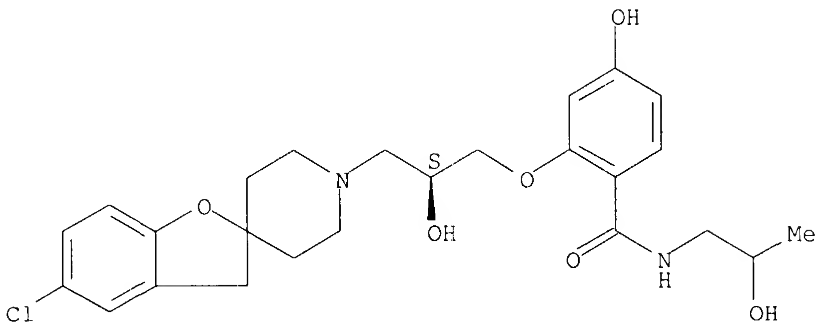


RN 644971-66-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxypropyl)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

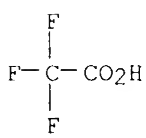
CRN 644971-65-3
CMF C25 H31 Cl N2 O6

Absolute stereochemistry.



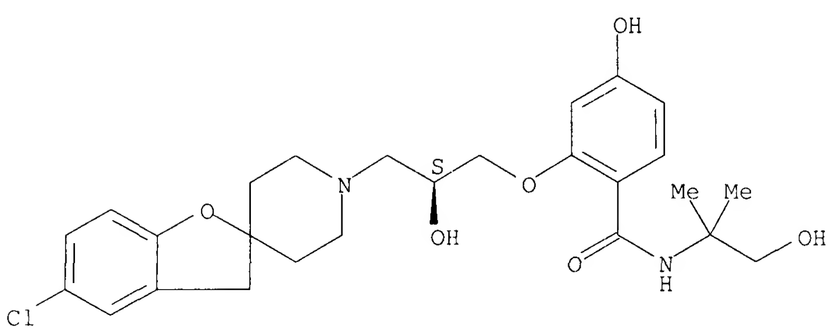
CM 2

CRN 76-05-1
CMF C2 H F3 O2



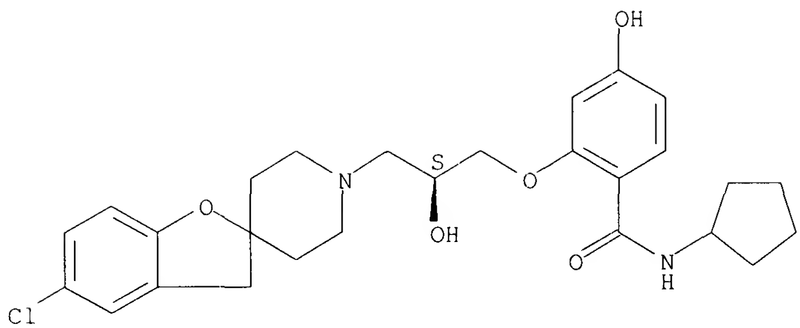
RN 644971-68-6 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxy-1,1-dimethylethyl)- (CA INDEX NAME)

Absolute stereochemistry.



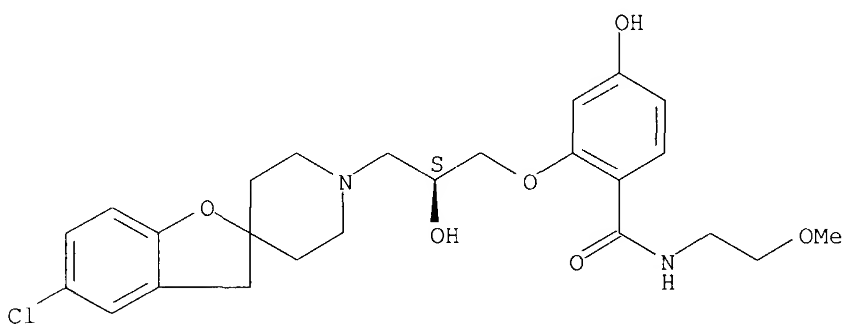
RN 644971-69-7 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-cyclopentyl-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



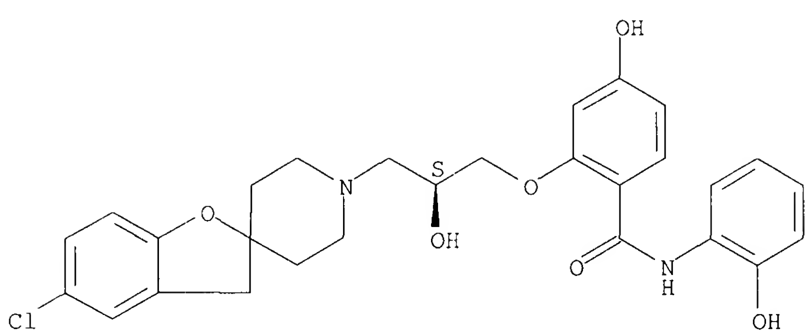
RN 644971-70-0 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-methoxyethyl)- (CA INDEX NAME)

Absolute stereochemistry.



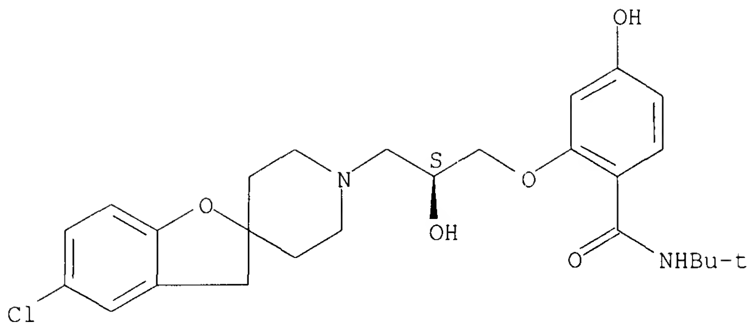
RN 644971-71-1 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxyphenyl)- (CA INDEX NAME)

Absolute stereochemistry.



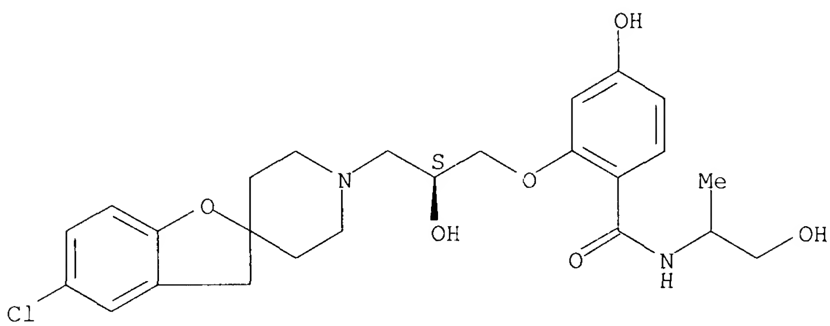
RN 644971-72-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(1,1-dimethylethyl)-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



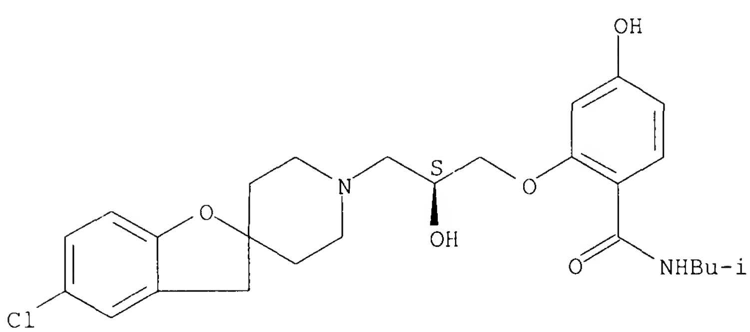
RN 644971-73-3 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxy-1-methylethyl)- (CA INDEX NAME)

Absolute stereochemistry.



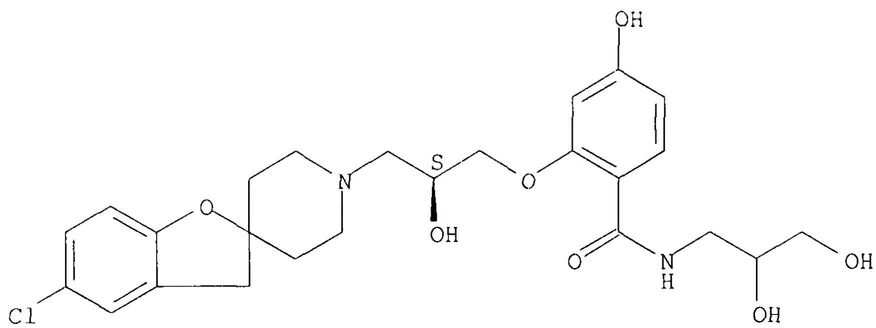
RN 644971-74-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-methylpropyl)- (CA INDEX NAME)

Absolute stereochemistry.



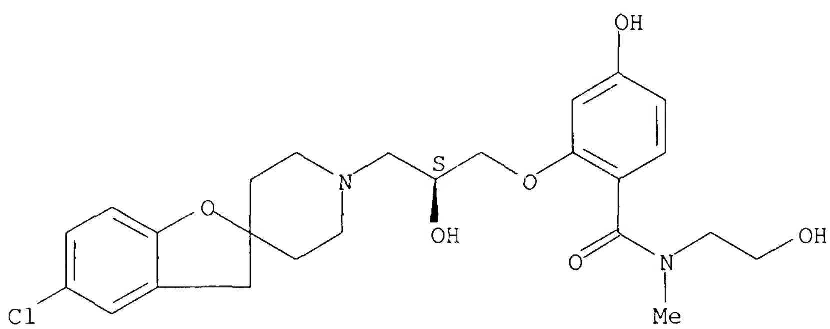
RN 644971-75-5 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(2,3-dihydroxypropyl)-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



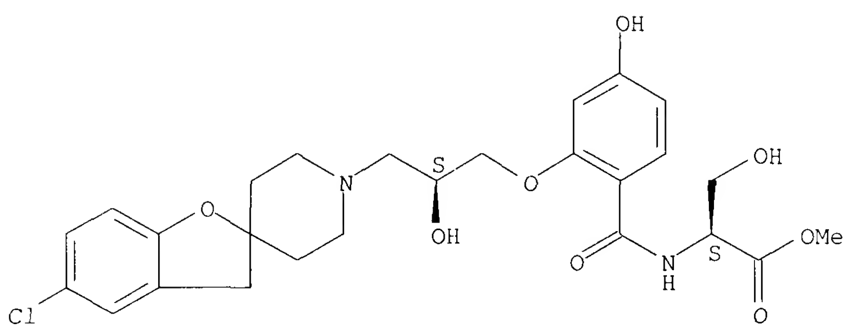
RN 644971-76-6 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxyethyl)-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



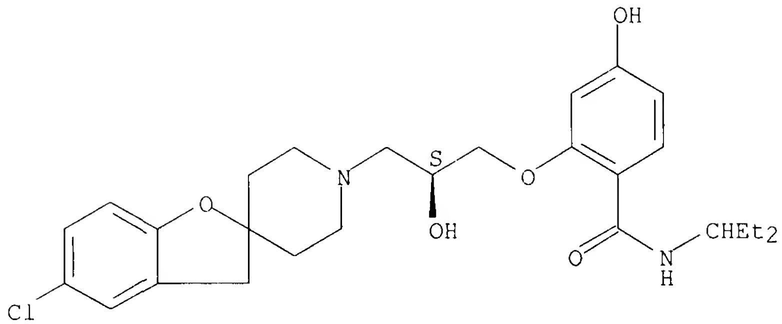
RN 644971-77-7 CAPLUS
CN L-Serine, N-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



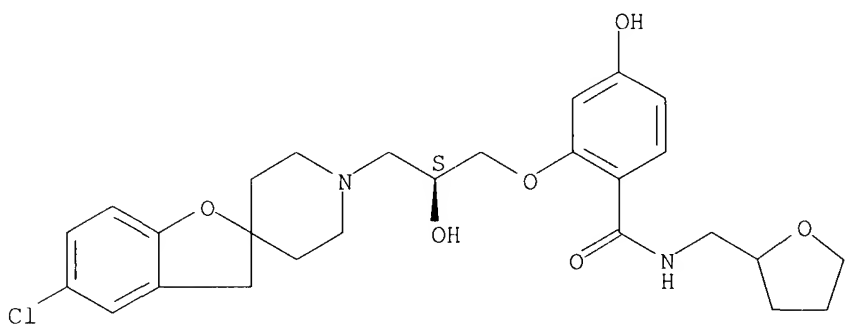
RN 644971-78-8 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(1-ethylpropyl)-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



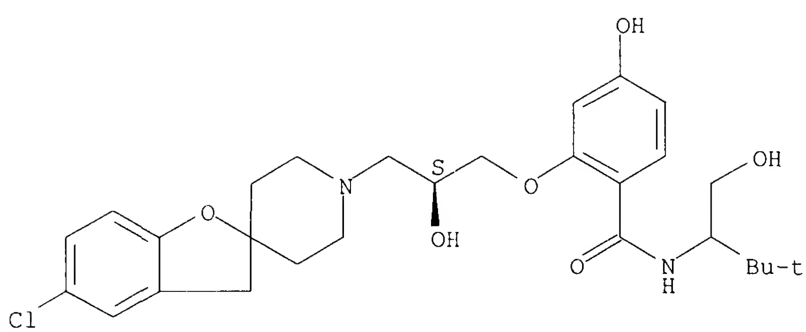
RN 644971-79-9 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-[(tetrahydro-2-furanyl)methyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-80-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-[1-(hydroxymethyl)-2,2-dimethylpropyl]- (CA INDEX NAME)

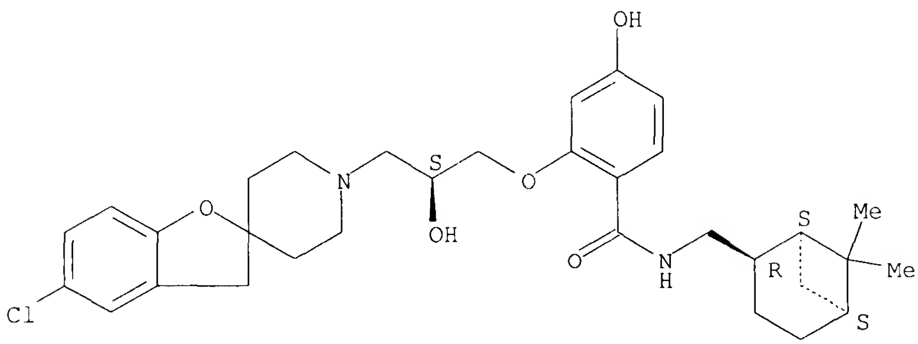
Absolute stereochemistry.



RN 644971-81-3 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-[[(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-

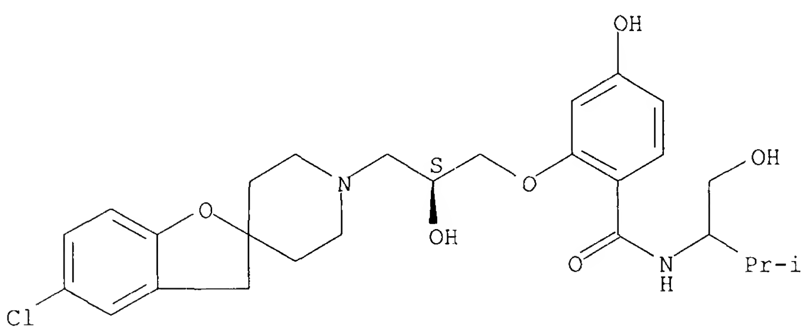
yl]methyl]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



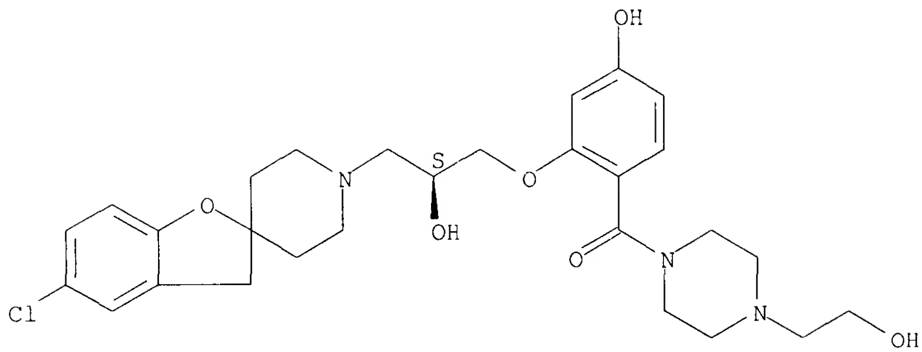
RN 644971-82-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-[1-(hydroxymethyl)-2-methylpropyl]- (CA INDEX NAME)

Absolute stereochemistry.



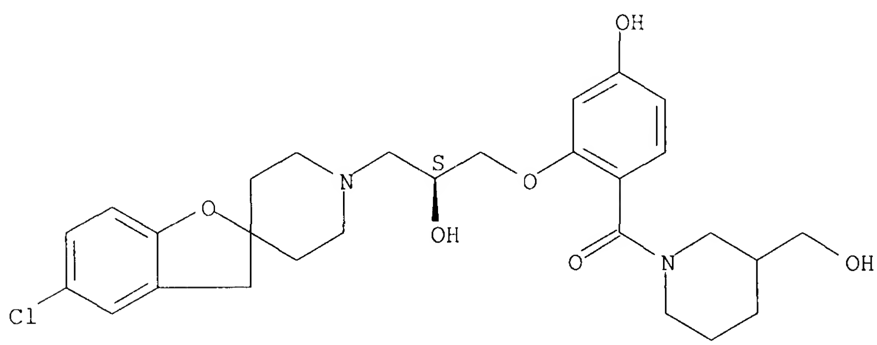
RN 644971-83-5 CAPLUS
CN 1-Piperazineethanol, 4-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



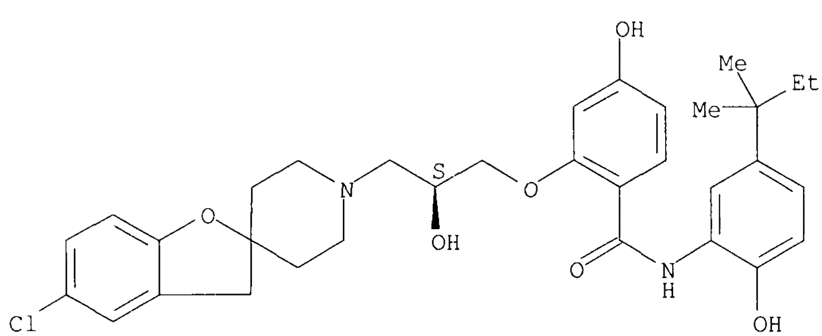
RN 644971-84-6 CAPLUS
CN 3-Piperidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-85-7 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-[5-(1,1-dimethylpropyl)-2-hydroxyphenyl]-4-hydroxy- (CA INDEX NAME)

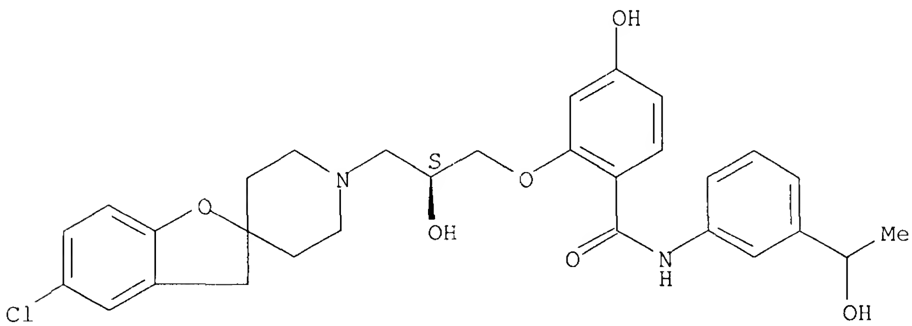
Absolute stereochemistry.



RN 644971-86-8 CAPLUS

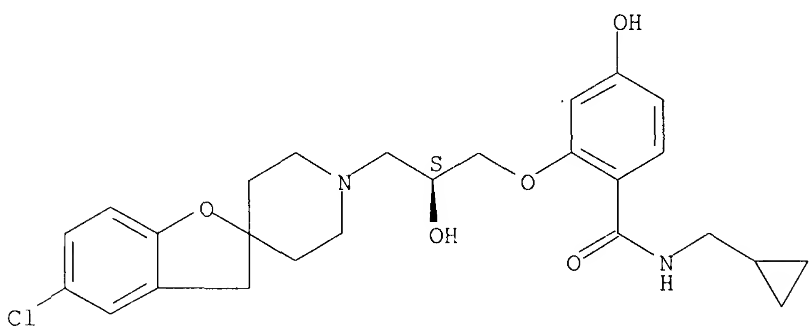
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-[3-(1-hydroxyethyl)phenyl]- (CA INDEX NAME)

Absolute stereochemistry.



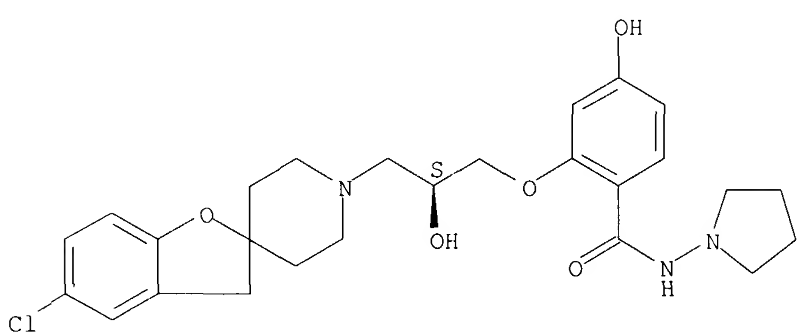
RN 644971-87-9 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(cyclopropylmethyl)-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-88-0 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-1-pyrrolidinyl- (CA INDEX NAME)

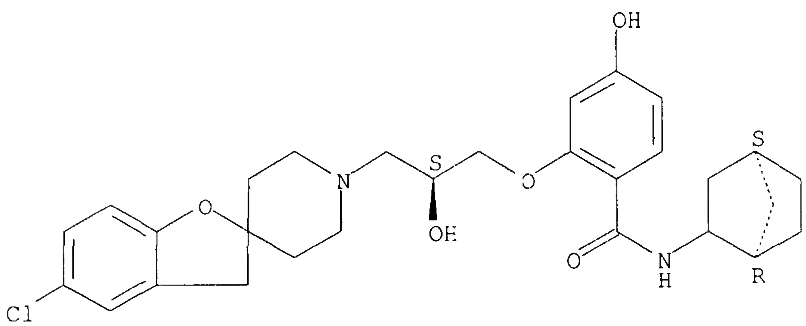
Absolute stereochemistry.



RN 644971-89-1 CAPLUS

CN Benzamide, N-(1R,4S)-bicyclo[2.2.1]hept-2-yl-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy- (CA INDEX NAME)

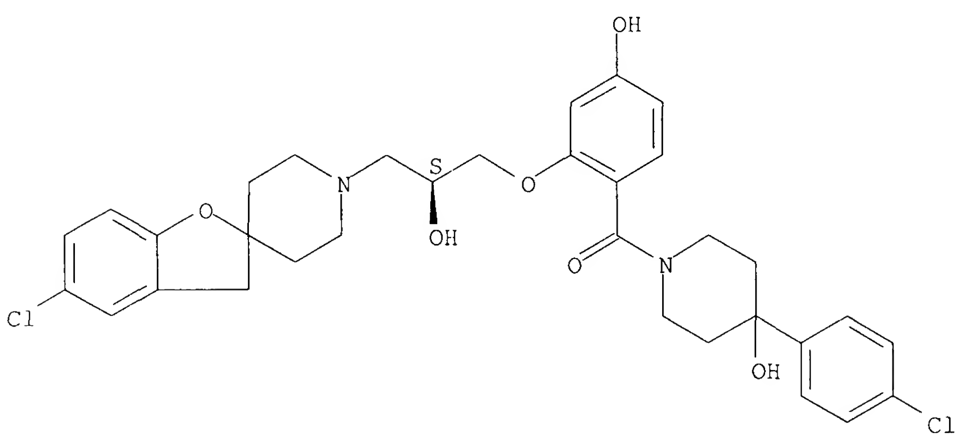
Absolute stereochemistry.



RN 644971-90-4 CAPLUS

CN 4-Piperidinol, 4-(4-chlorophenyl)-1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

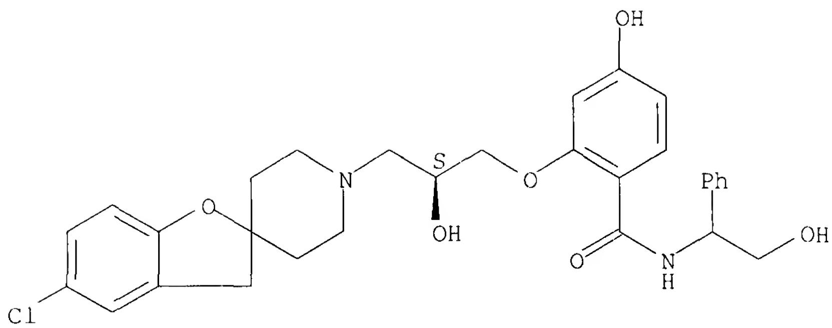
Absolute stereochemistry.



RN 644971-91-5 CAPLUS

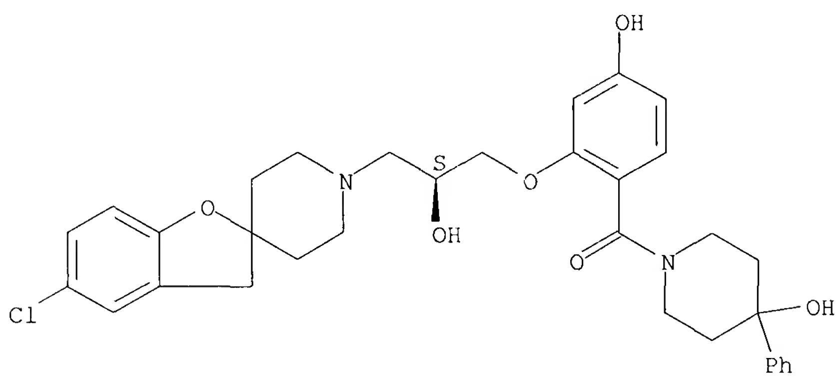
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxy-1-phenylethyl)- (CA INDEX NAME)

Absolute stereochemistry.



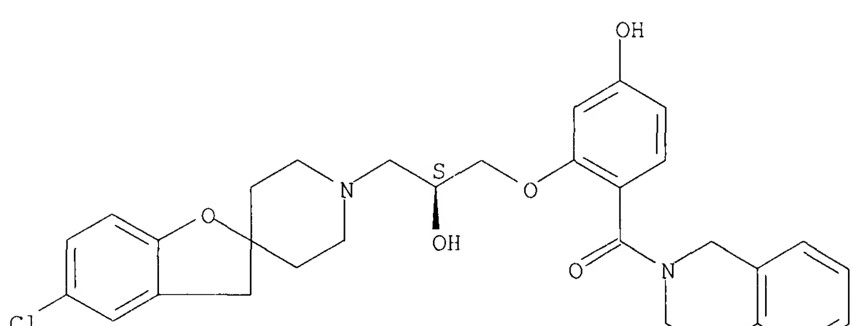
RN 644971-92-6 CAPLUS
CN 4-Piperidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



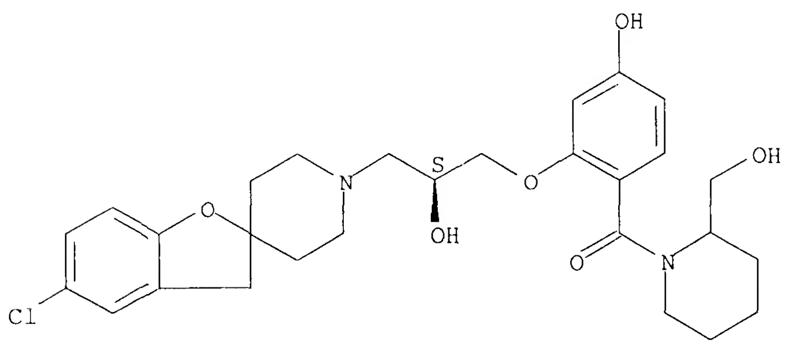
RN 644971-93-7 CAPLUS
CN Isoquinoline, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



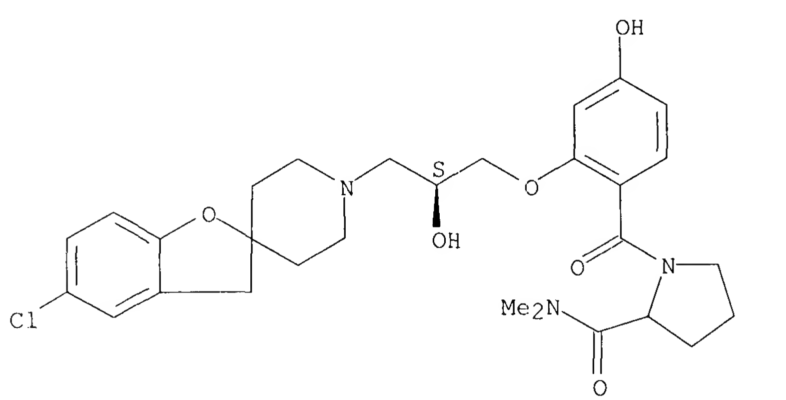
RN 644971-94-8 CAPLUS
CN 2-Piperidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



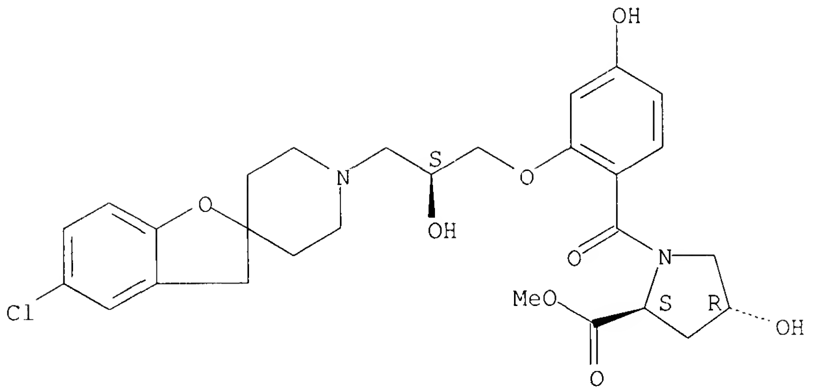
RN 644971-95-9 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-N,N-dimethyl- (CA INDEX NAME)

Absolute stereochemistry.



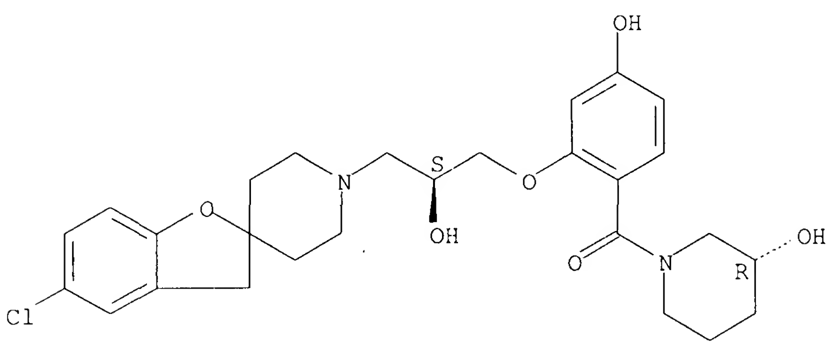
RN 644971-96-0 CAPLUS
CN L-Proline, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-hydroxy-, methyl ester, (4R)- (CA INDEX NAME)

Absolute stereochemistry.



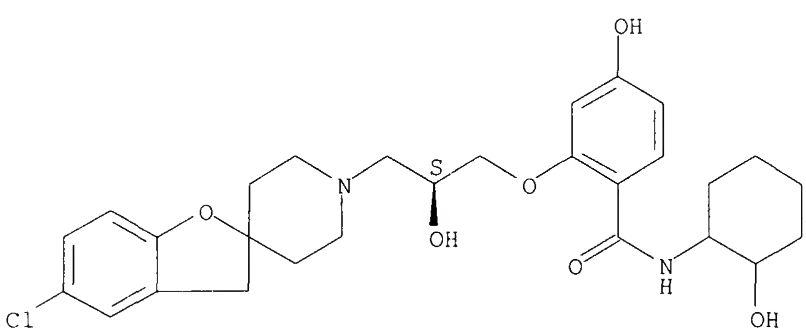
RN 644971-97-1 CAPLUS
CN 3-Piperidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-98-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(2-hydroxycyclohexyl)- (CA INDEX NAME)

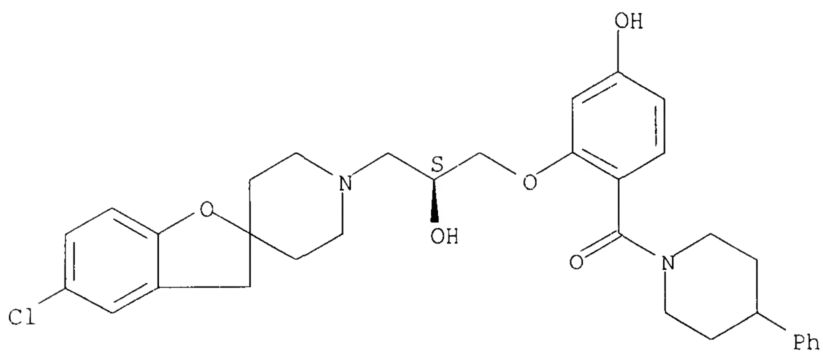
Absolute stereochemistry.



RN 644971-99-3 CAPLUS
CN Piperidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-

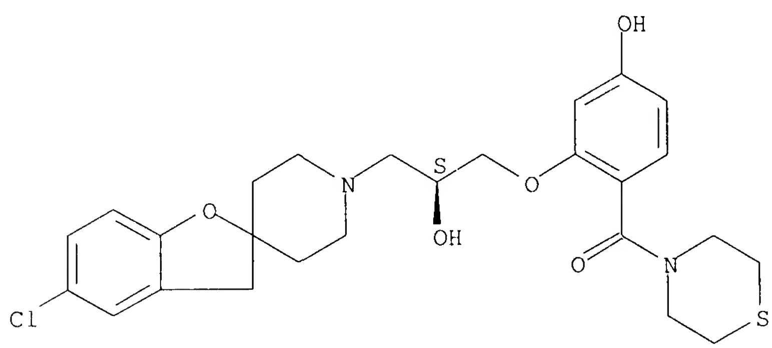
yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



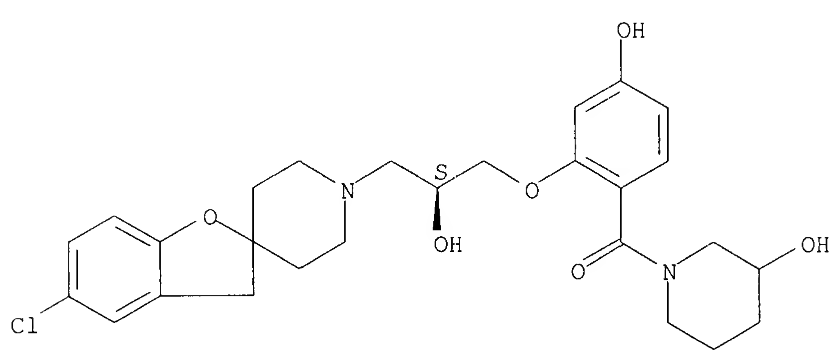
RN 644972-00-9 CAPLUS
CN Thiomorpholine, 4-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



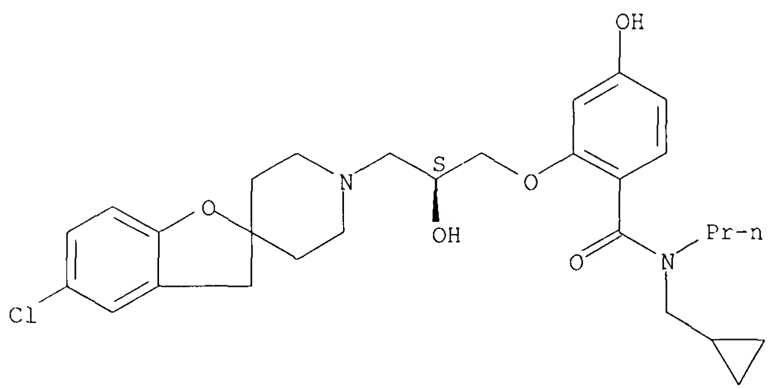
RN 644972-01-0 CAPLUS
CN 3-Piperidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



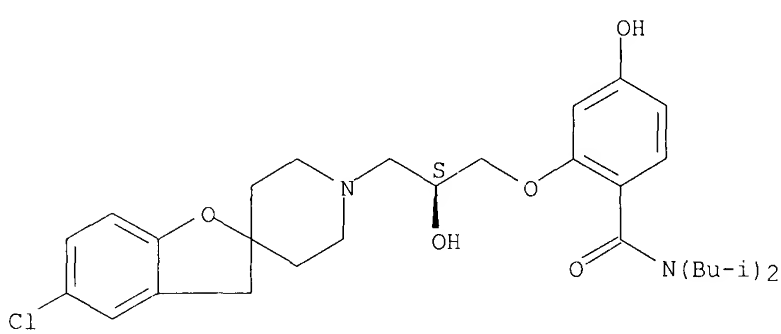
RN 644972-02-1 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(cyclopropylmethyl)-4-hydroxy-N-propyl- (CA INDEX NAME)

Absolute stereochemistry.



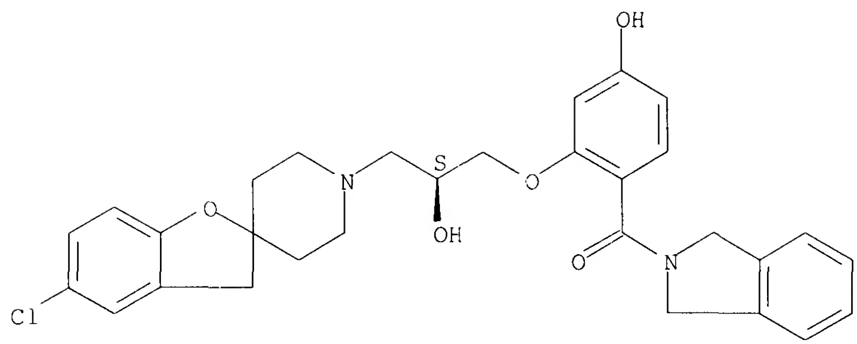
RN 644972-03-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N,N-bis(2-methylpropyl)- (CA INDEX NAME)

Absolute stereochemistry.



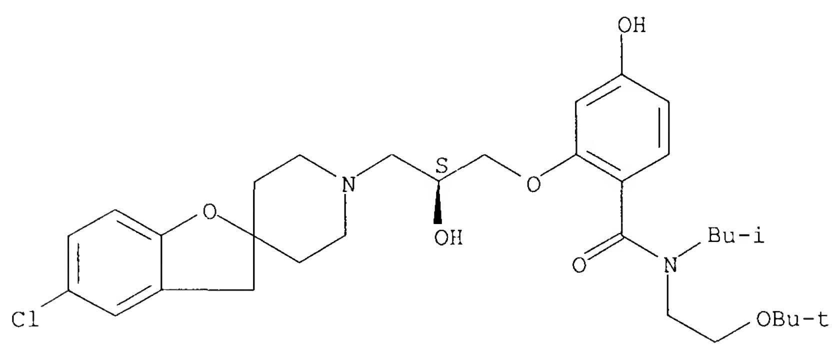
RN 644972-04-3 CAPLUS
CN 1H-Isoindole, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-2,3-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



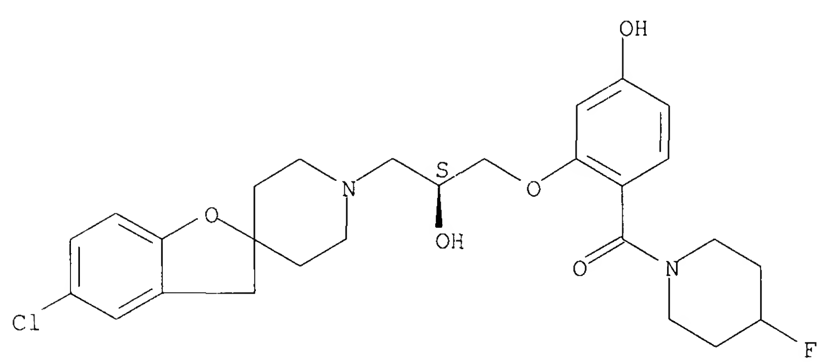
RN 644972-05-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-[2-(1,1-dimethylethoxy)ethyl]-4-hydroxy-N-(2-methylpropyl)- (CA INDEX NAME)

Absolute stereochemistry.



RN 644972-06-5 CAPLUS
CN Piperidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4-fluoro- (9CI) (CA INDEX NAME)

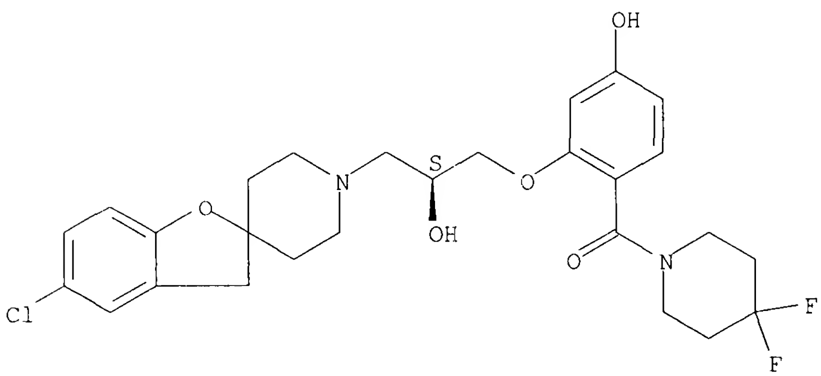
Absolute stereochemistry.



RN 644972-07-6 CAPLUS

CN   Piperidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-4,4-difluoro- (9CI) (CA INDEX NAME)

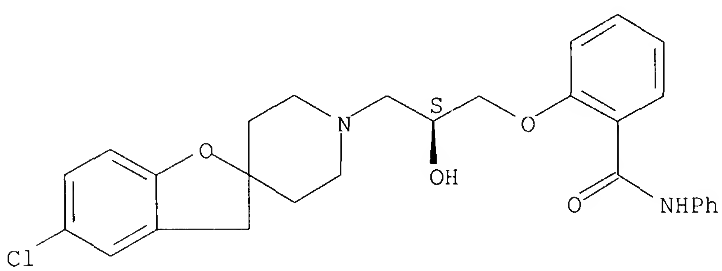
Absolute stereochemistry.



RN   644972-08-7   CAPLUS

CN   Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-phenyl- (CA INDEX NAME)

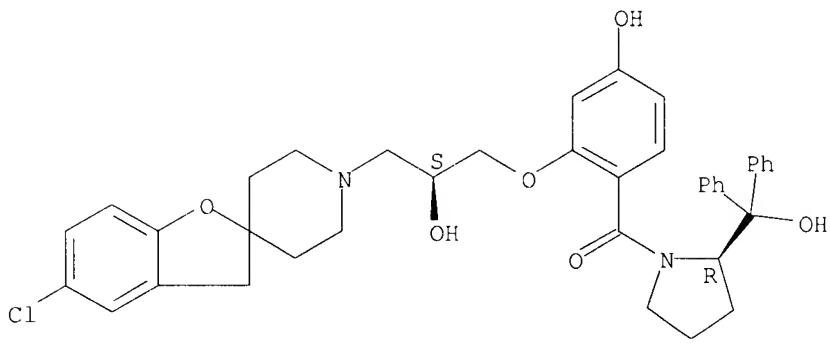
Absolute stereochemistry.



RN   644972-09-8   CAPLUS

CN   2-Pyrrolidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-α,α-diphenyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

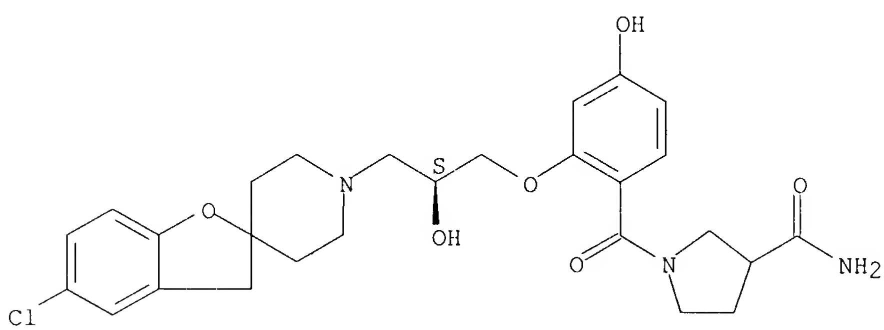


RN 644972-54-3 CAPLUS
CN 3-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

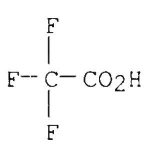
CRN 644972-53-2
CMF C27 H32 Cl N3 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

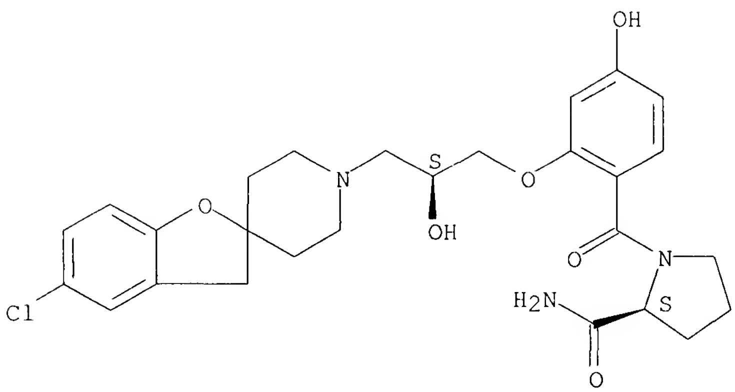


RN 644972-59-8 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (2S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

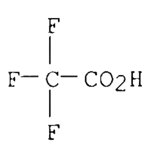
CRN 644972-58-7
CMF C27 H32 Cl N3 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

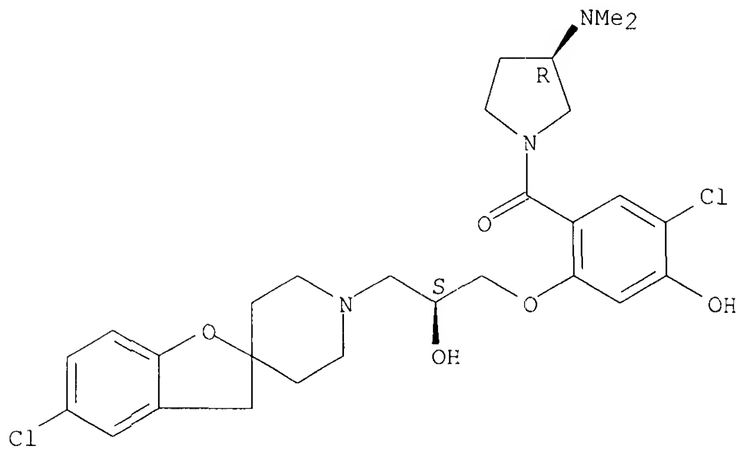


RN 644972-63-4 CAPLUS
CN 3-Pyrrolidinamine, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-N,N-dimethyl-, (3R)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

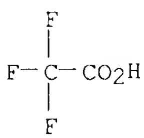
CRN 644972-62-3
CMF C28 H35 Cl2 N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

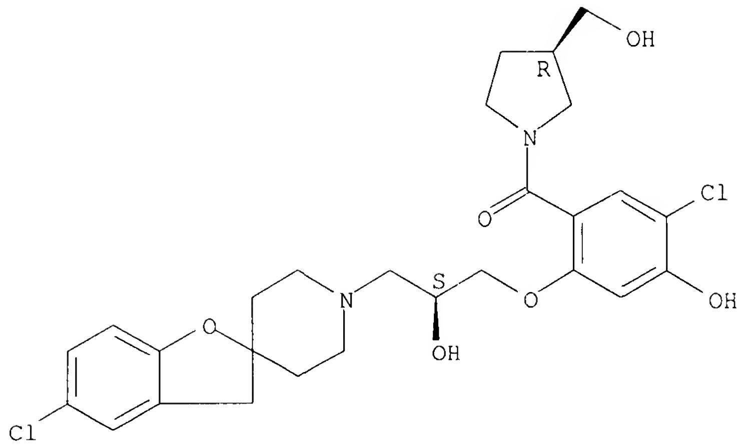


RN 644972-66-7 CAPLUS
CN 3-Pyrrolidinemethanol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3R)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

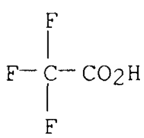
CRN 644972-65-6
CMF C27 H32 Cl2 N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

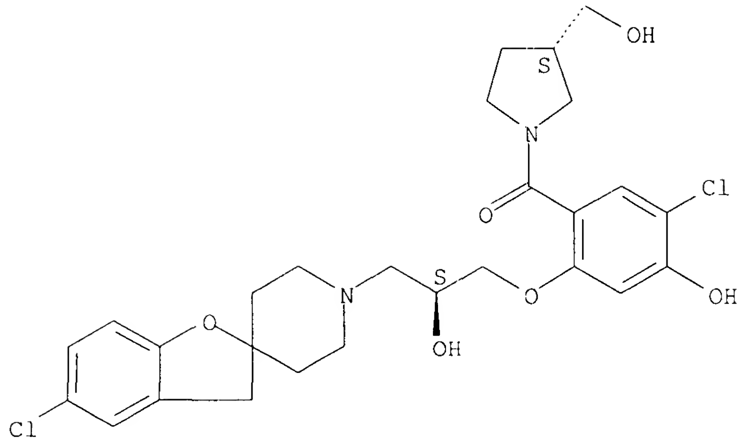


RN 644972-69-0 CAPLUS
CN 3-Pyrrolidinemethanol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

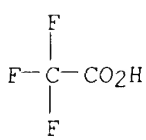
CRN 644972-68-9
CMF C27 H32 Cl2 N2 O6

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

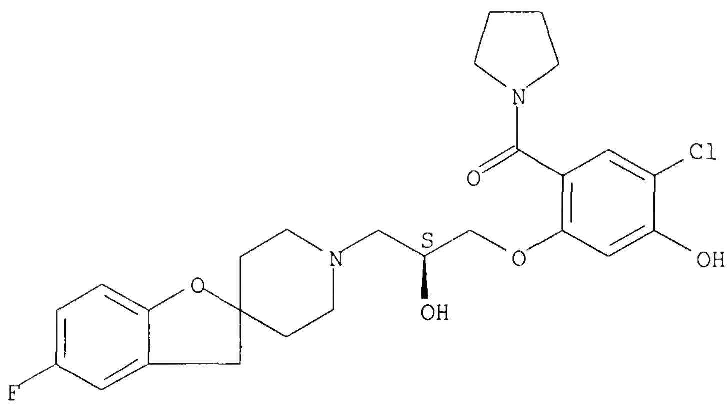


RN 644972-71-4 CAPLUS
CN Pyrrolidine, 1-[5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

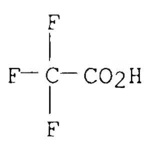
CRN 644972-70-3
CMF C26 H30 Cl F N2 O5

Absolute stereochemistry.



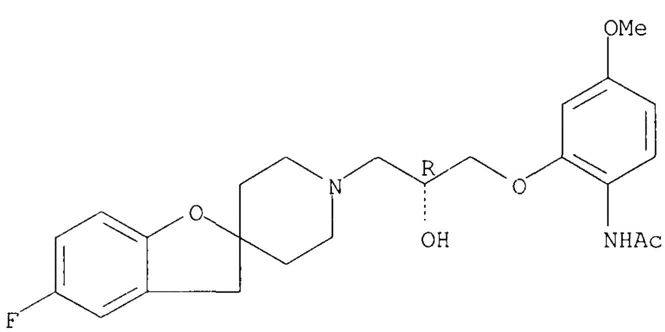
CM 2

CRN 76-05-1
CMF C2 H F3 O2



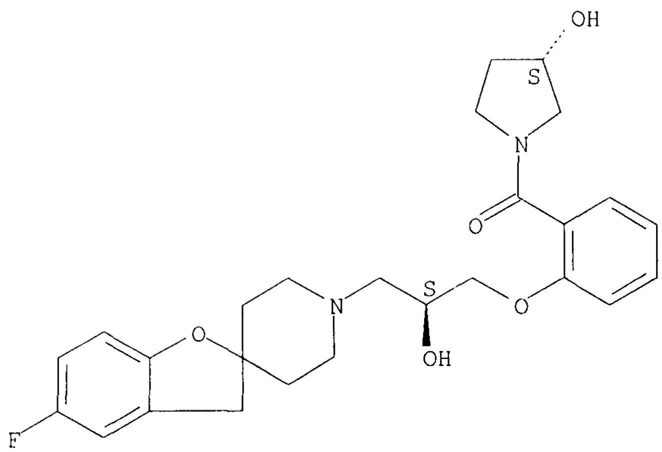
RN 644972-75-8 CAPLUS
CN Acetamide, N-[2-[(2R)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methoxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



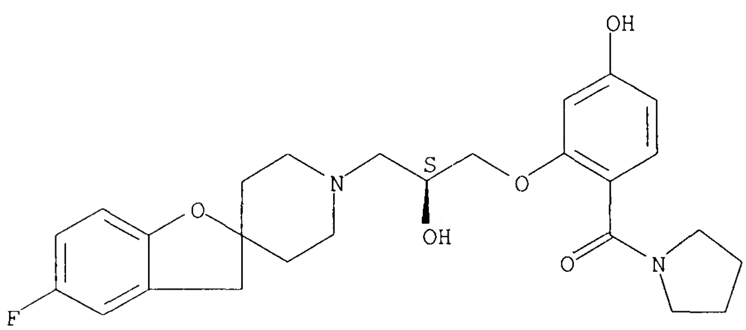
RN 644972-81-6 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



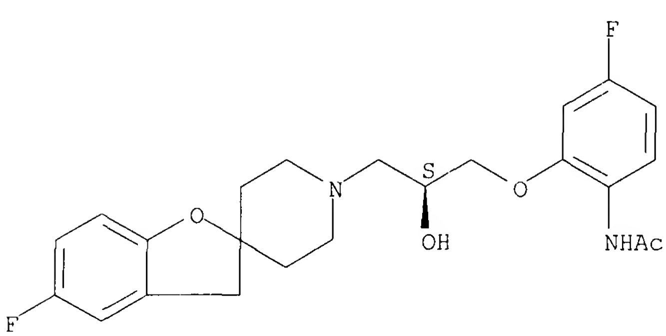
RN 644972-82-7 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxybenzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



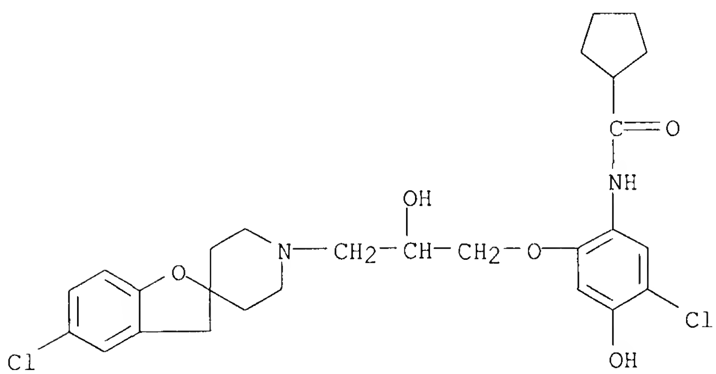
RN 644972-86-1 CAPLUS
CN Acetamide, N-[4-fluoro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)

Absolute stereochemistry.

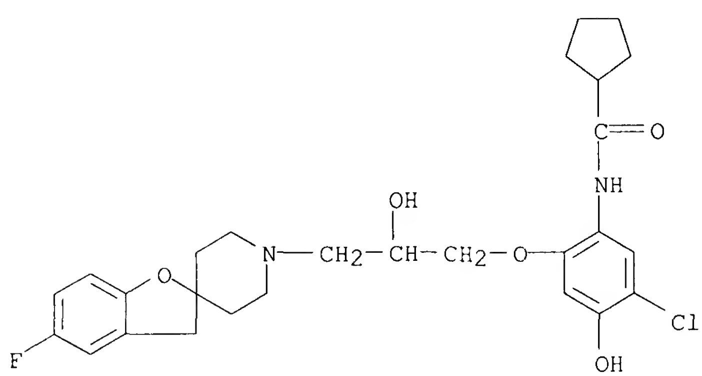


RN 644972-87-2 CAPLUS

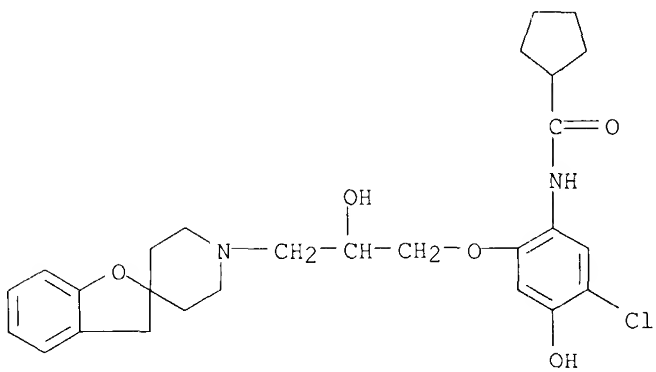
CN Cyclopentanecarboxamide, N-[5-chloro-2-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)



RN 644972-92-9 CAPLUS
CN Cyclopentanecarboxamide, N-[5-chloro-2-[3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)



RN 644972-93-0 CAPLUS
CN Cyclopentanecarboxamide, N-[5-chloro-4-hydroxy-2-(2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy)phenyl]- (9CI) (CA INDEX NAME)

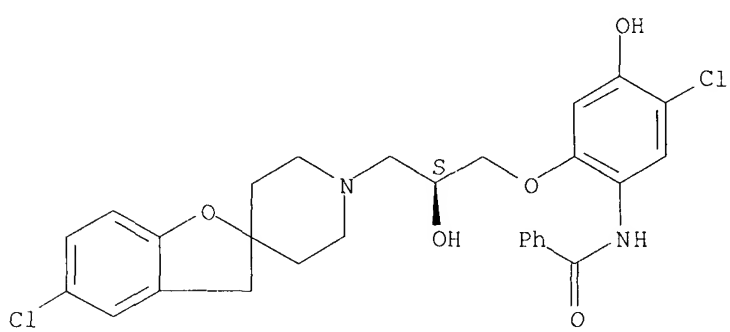


RN 644972-95-2 CAPLUS
CN Benzamide, N-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

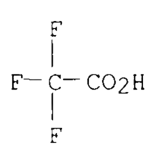
CRN 644972-94-1
CMF C28 H28 Cl2 N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

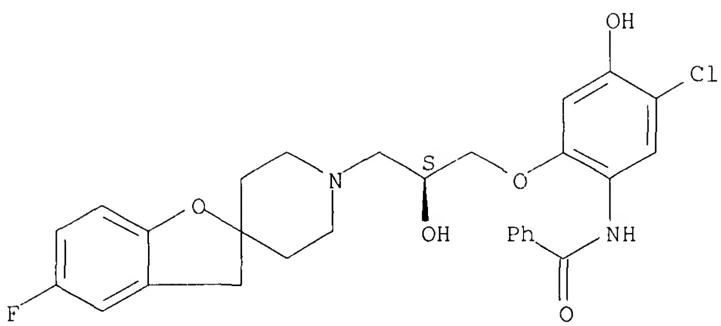


RN 644973-01-3 CAPLUS
CN Benzamide, N-[5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

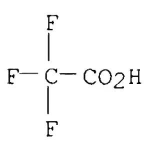
CRN 644973-00-2
CMF C28 H28 Cl F N2 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

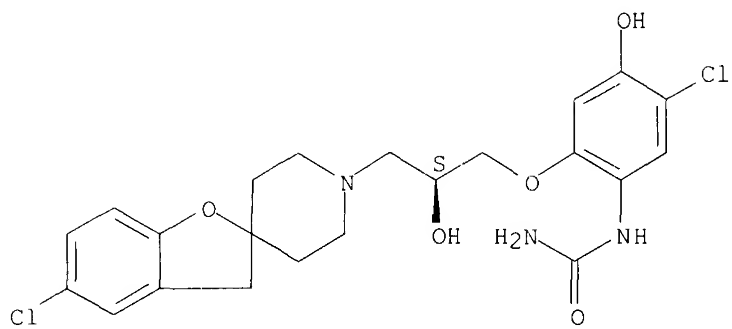


RN 644973-03-5 CAPLUS
CN Urea, [5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

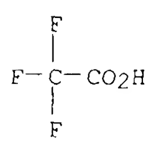
CRN 644973-02-4
CMF C22 H25 Cl2 N3 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

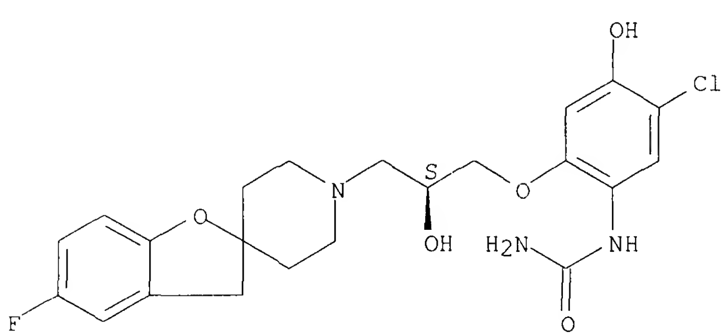


RN 644973-06-8 CAPLUS
CN Urea, [5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

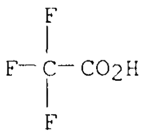
CRN 644973-05-7
CMF C22 H25 Cl F N3 O5

Absolute stereochemistry.



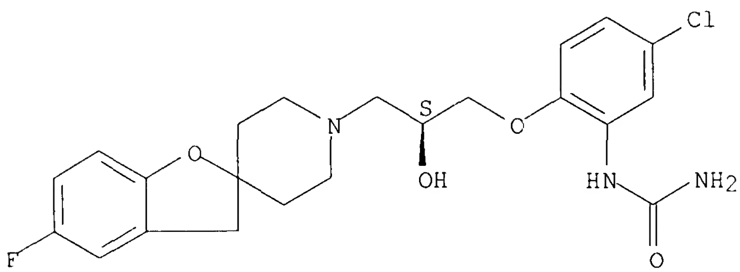
CM 2

CRN 76-05-1
CMF C2 H F3 O2



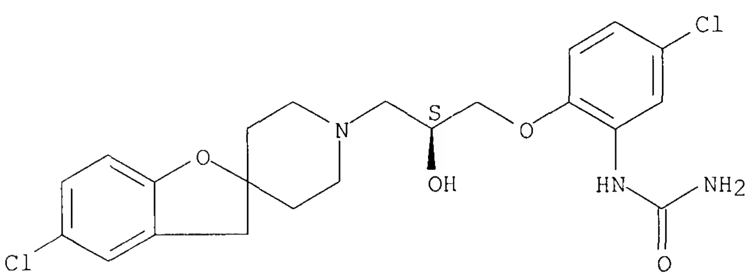
RN 644973-08-0 CAPLUS
CN Urea, [5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



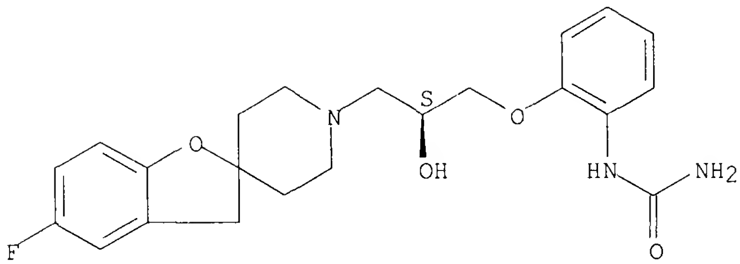
RN 644973-10-4 CAPLUS
CN Urea, [5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



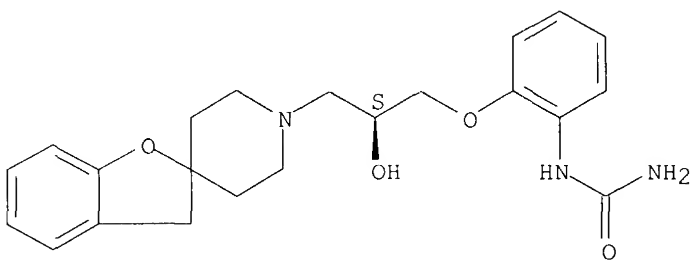
RN 644973-11-5 CAPLUS
CN Urea, [2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



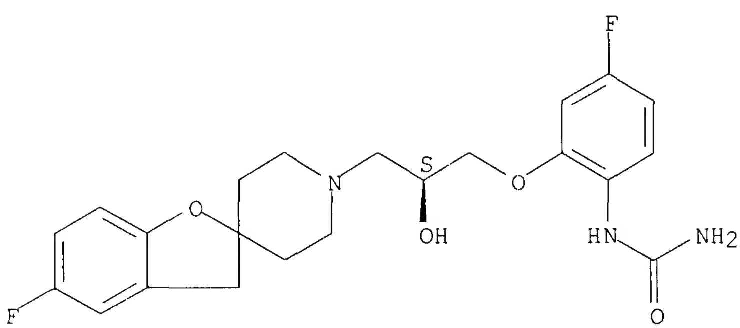
RN 644973-12-6 CAPLUS
CN Urea, [2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



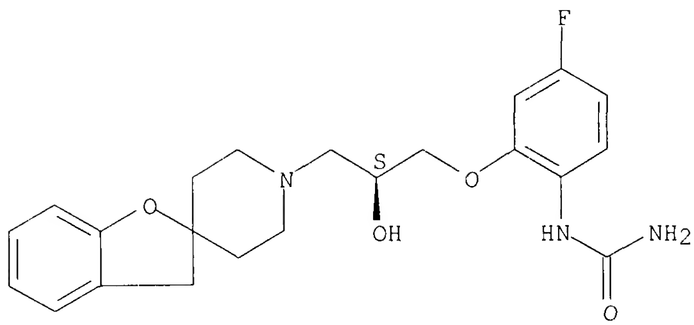
RN 644973-13-7 CAPLUS
CN Urea, [4-fluoro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



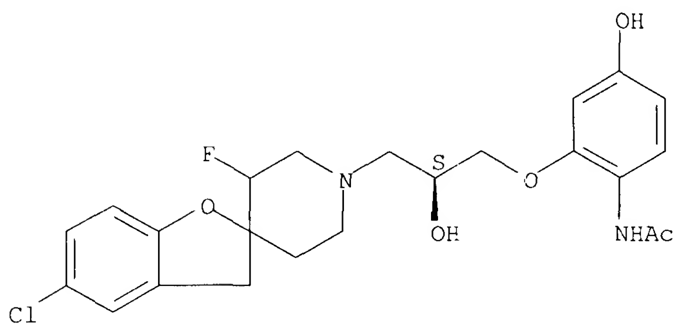
RN 644973-14-8 CAPLUS
CN Urea, [4-fluoro-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



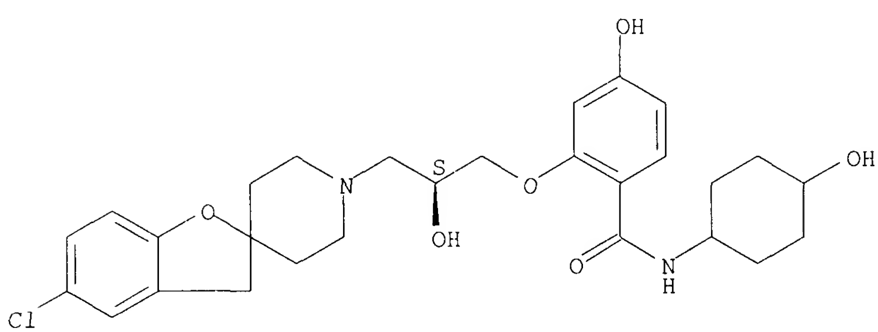
RN 644973-39-7 CAPLUS
CN Acetamide, N-[2-[(2S)-3-(5-chloro-3'-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxyphenyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 645389-76-0 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy-N-(4-hydroxycyclohexyl)- (CA INDEX NAME)

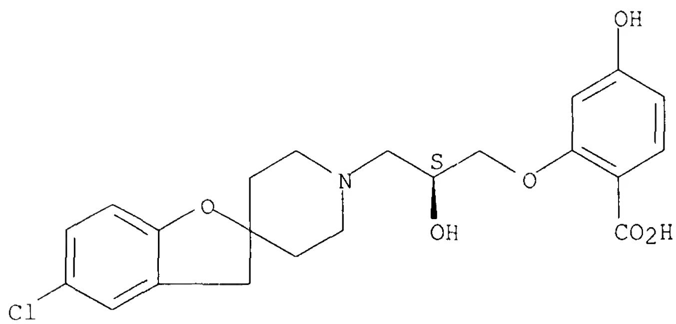
Absolute stereochemistry.



IT 644969-54-0 644969-92-6 644970-60-5
644970-97-8 644973-07-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

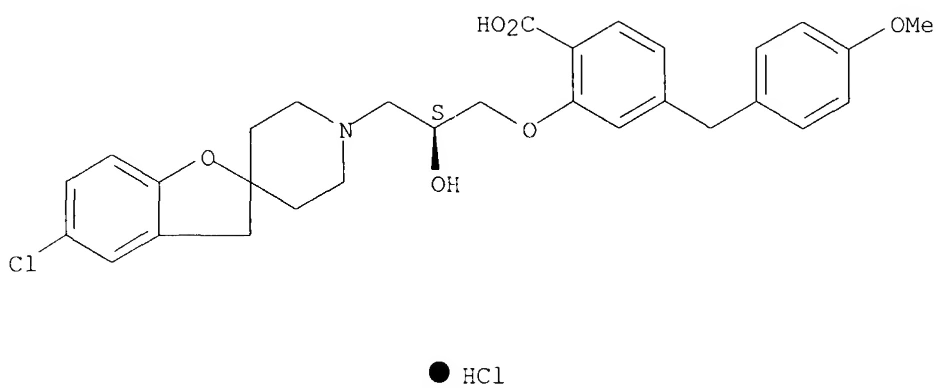
RN 644969-54-0 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.



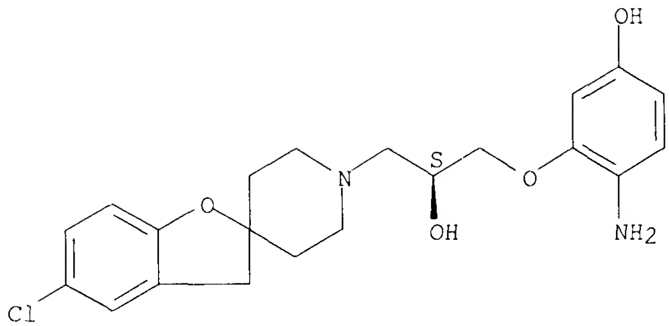
RN 644969-92-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



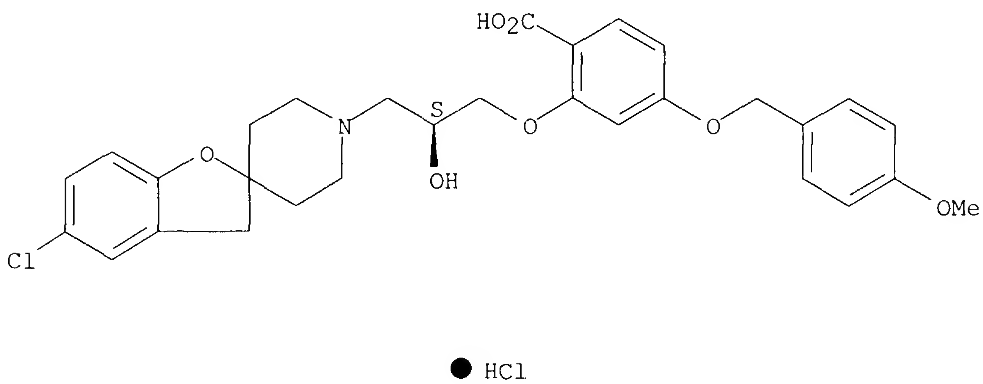
RN 644970-60-5 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-amino-5-hydroxyphenoxy)methyl]-5-chloro-, (αS)- (CA INDEX NAME)

Absolute stereochemistry.



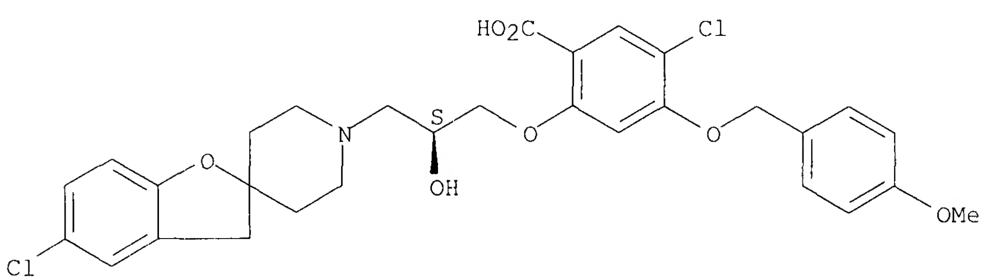
RN 644970-97-8 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644973-07-9 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



IT 644969-14-2P 644969-23-3P 644969-26-6P
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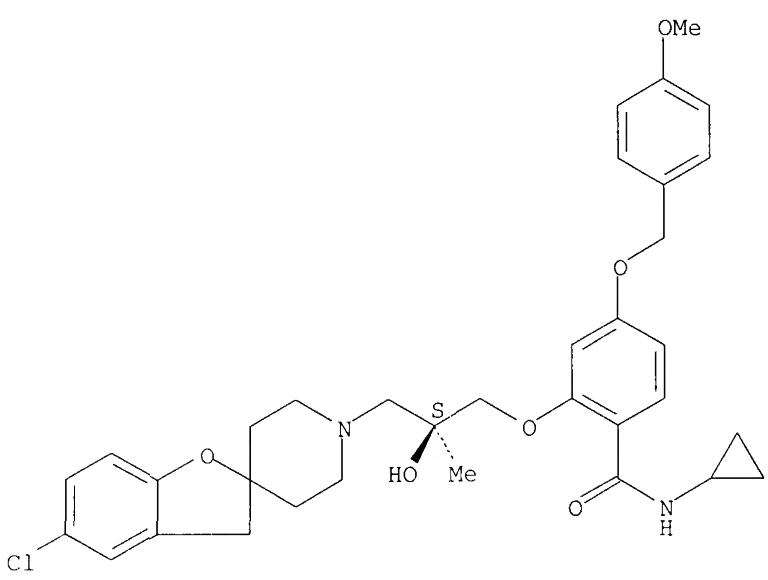
644972-73-6P 644972-74-7P 644972-83-8P
644972-84-9P 644972-85-0P 644972-91-8P
644973-04-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tricyclic spiropiperidines or spiropyrrolidines useful against disorders affected by modulation of chemokine receptors)

RN 644969-14-2 CAPLUS

CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-N-cyclopropyl-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

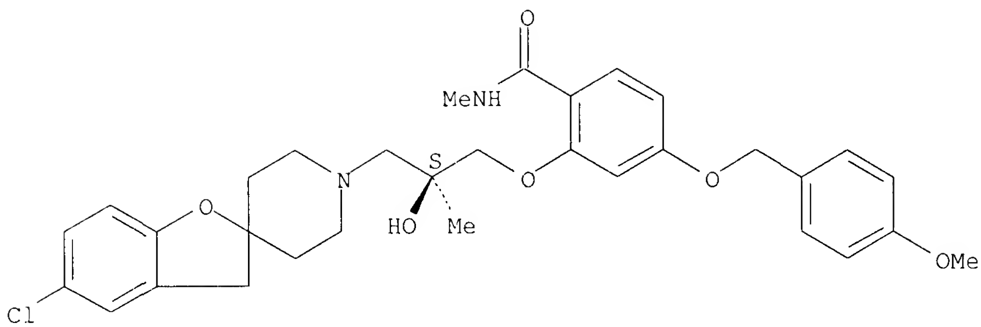
Absolute stereochemistry.



RN 644969-23-3 CAPLUS

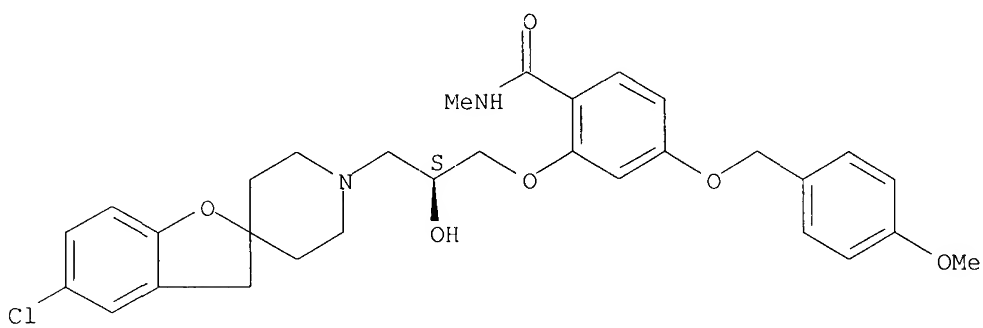
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



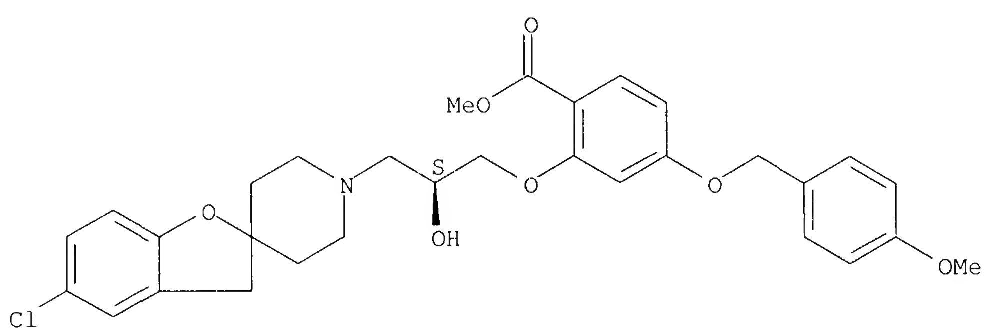
RN 644969-26-6 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



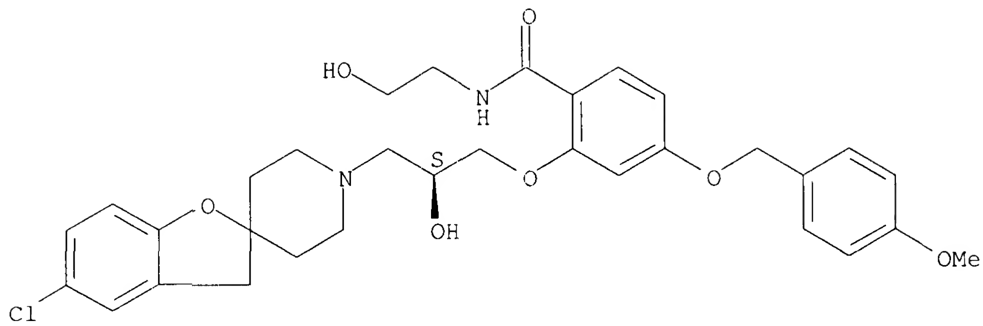
RN 644969-50-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



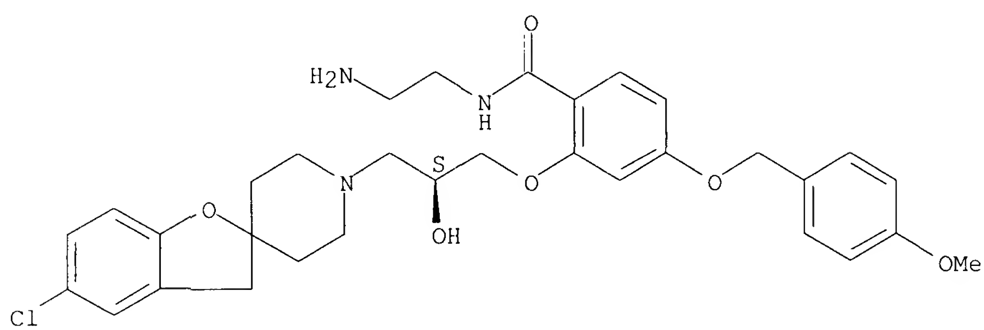
RN 644969-51-7 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(2-hydroxyethyl)-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



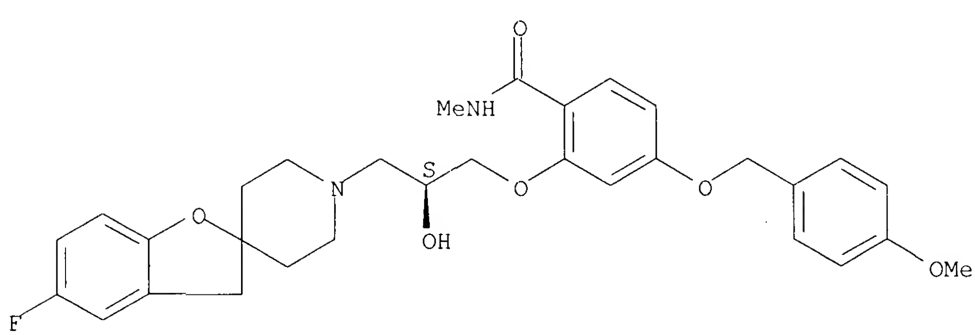
RN 644969-53-9 CAPLUS
CN Benzamide, N-(2-aminoethyl)-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



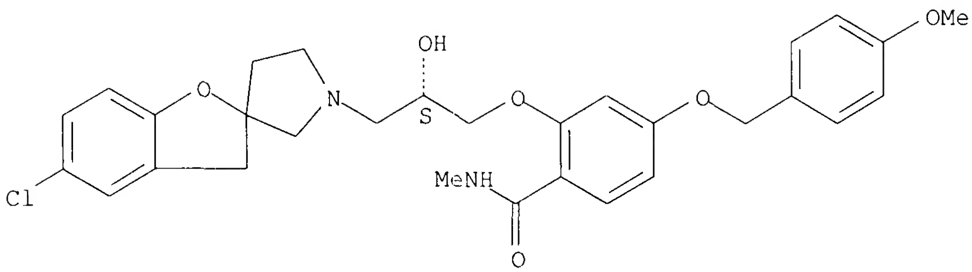
RN 644969-56-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



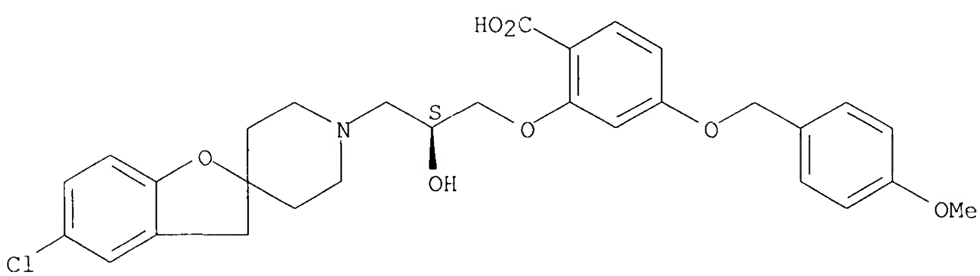
RN 644969-66-4 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),3'-pyrrolidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



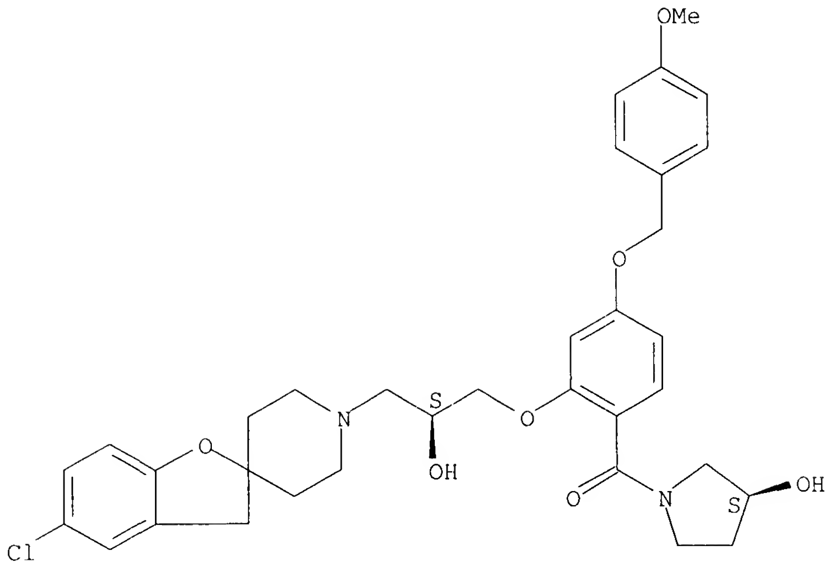
RN 644969-68-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



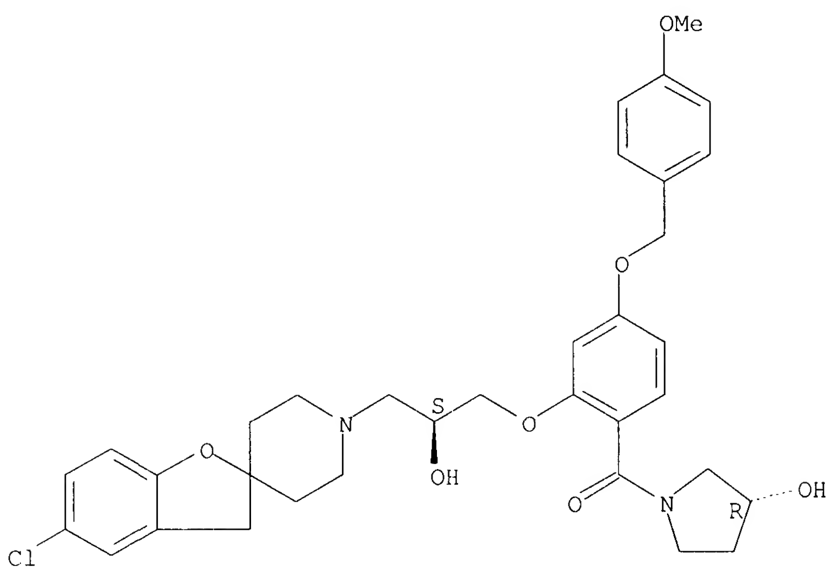
RN 644969-70-0 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



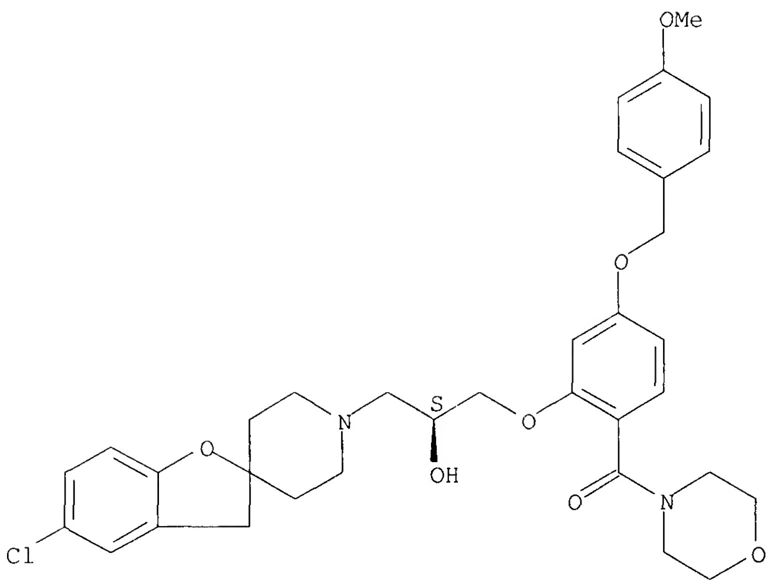
RN 644969-72-2 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (3R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



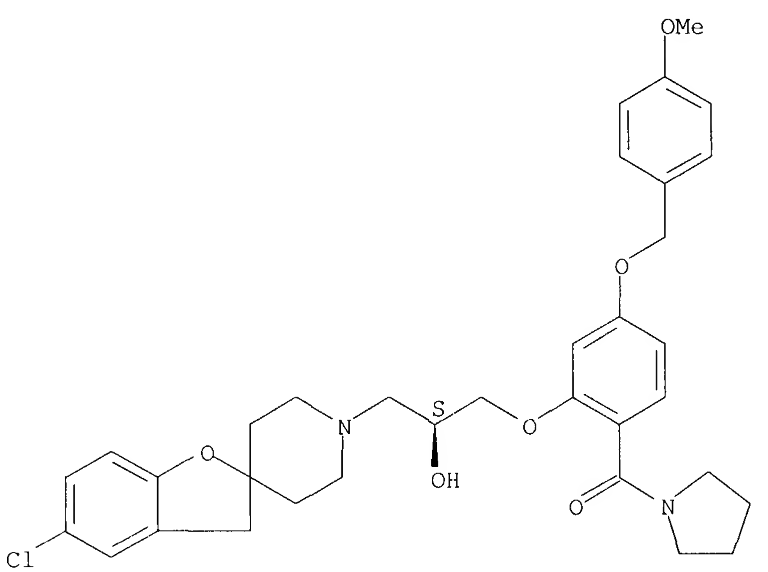
RN 644969-74-4 CAPLUS
CN Morpholine, 4-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



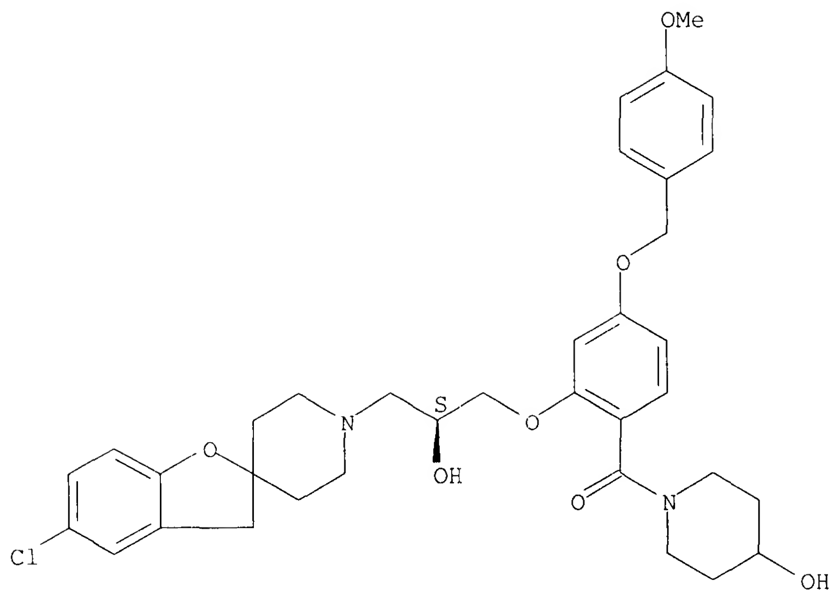
RN 644969-91-5 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



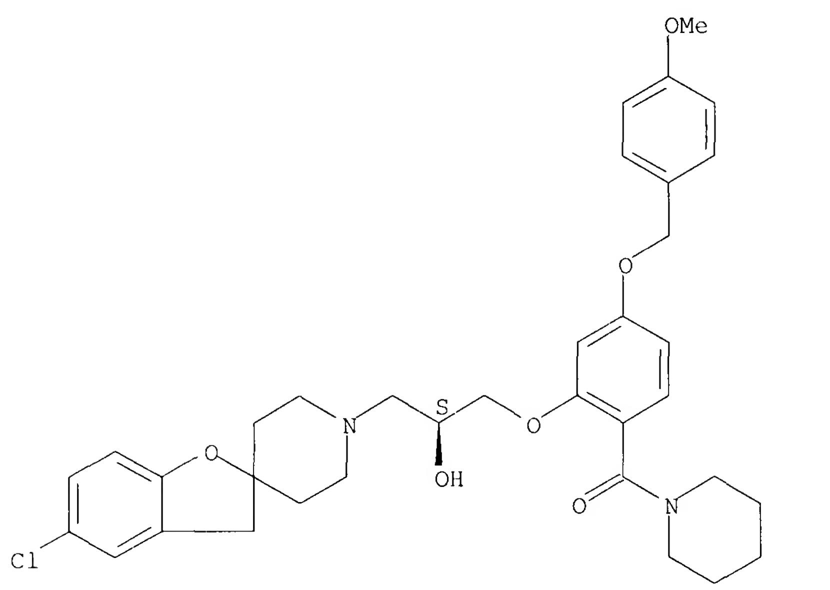
RN 644969-94-8 CAPLUS
CN 4-Piperidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



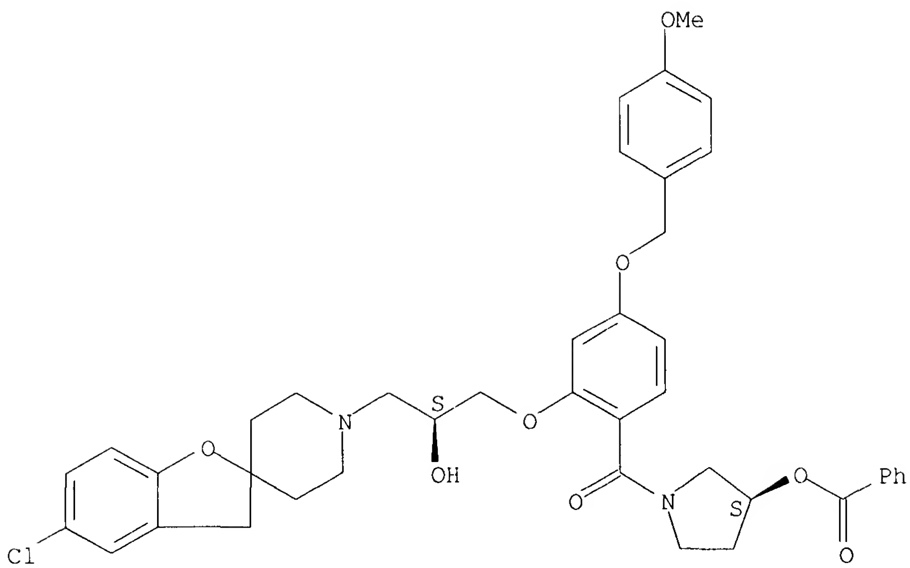
RN 644969-97-1 CAPLUS
CN Piperidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



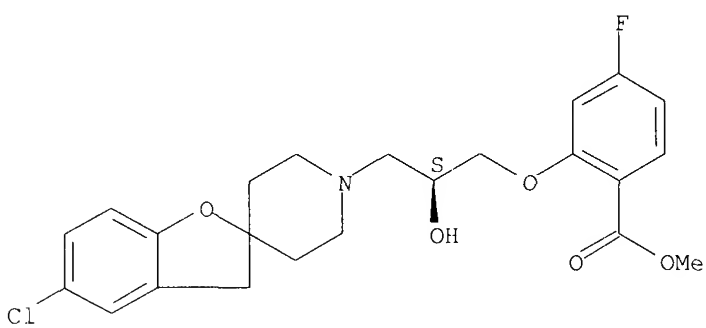
RN 644970-07-0 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, benzoate (ester), (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



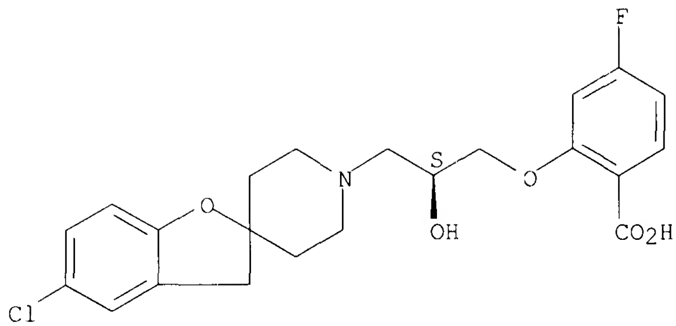
RN 644970-10-5 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluoro-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-11-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-fluoro-, hydrochloride (9CI) (CA INDEX NAME)

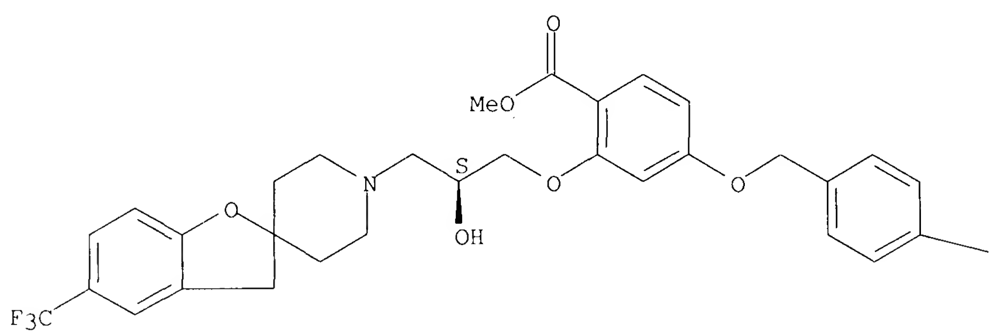
Absolute stereochemistry.



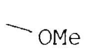
RN 644970-13-8 CAPLUS
CN Benzoic acid, 2-[(2S)-2-hydroxy-3-[5-(trifluoromethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]propoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



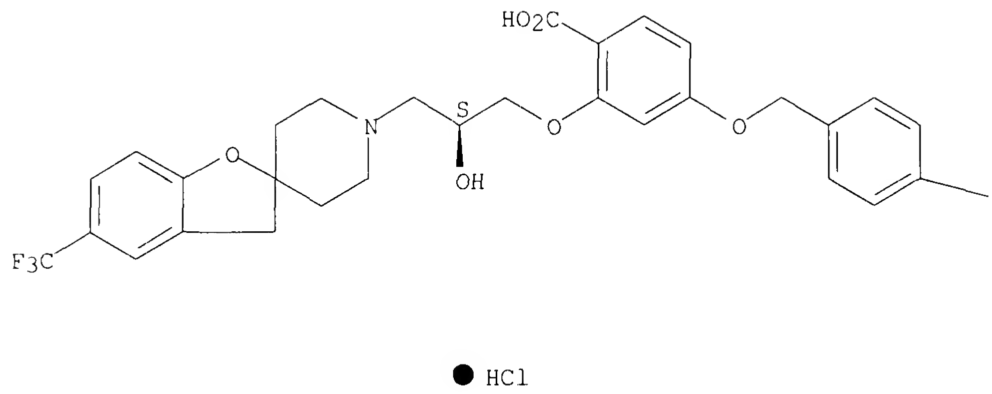
PAGE 1-B



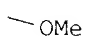
RN 644970-14-9 CAPLUS
CN Benzoic acid, 2-[(2S)-2-hydroxy-3-[5-(trifluoromethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]propoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

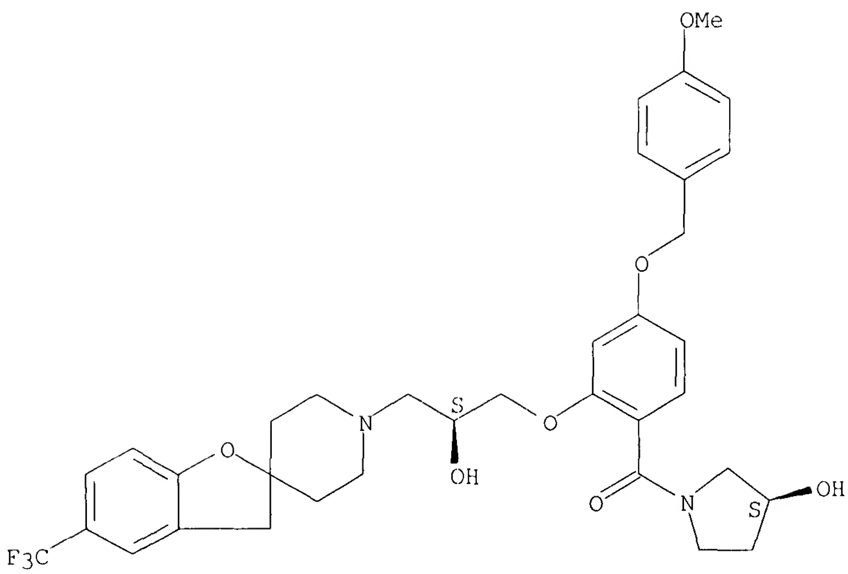


PAGE 1-B



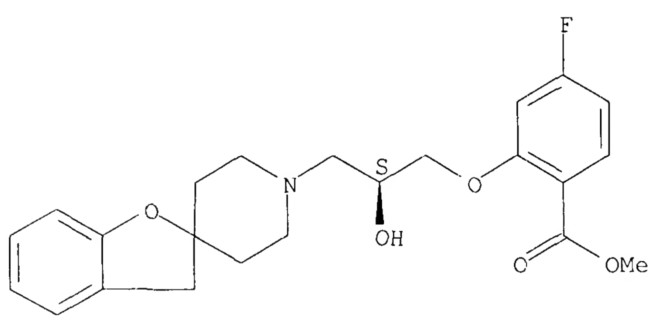
RN 644970-15-0 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-2-hydroxy-3-[5-(trifluoromethyl)spiro[benzofuran-2(3H),4'-piperidin]-1'-yl]propoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



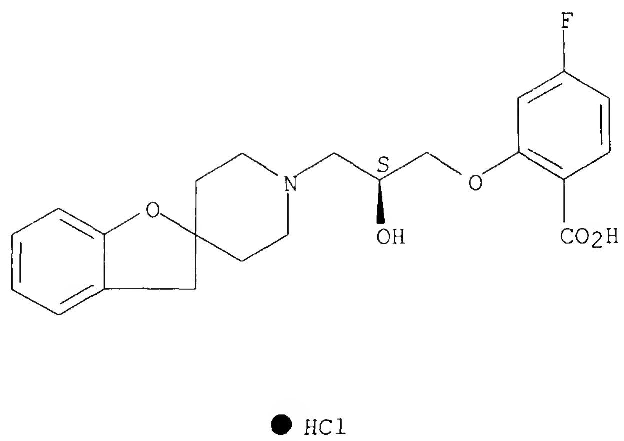
RN 644970-17-2 CAPLUS
CN Benzoic acid, 4-fluoro-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



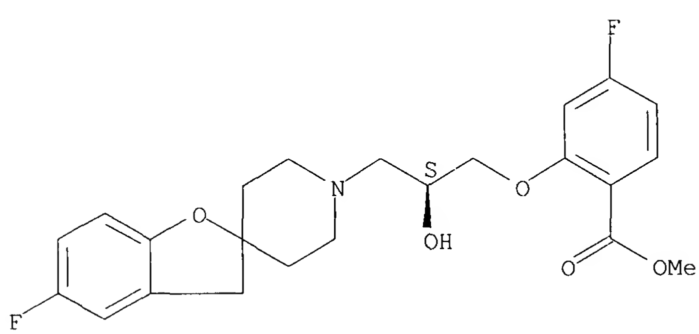
RN 644970-18-3 CAPLUS
CN Benzoic acid, 4-fluoro-2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



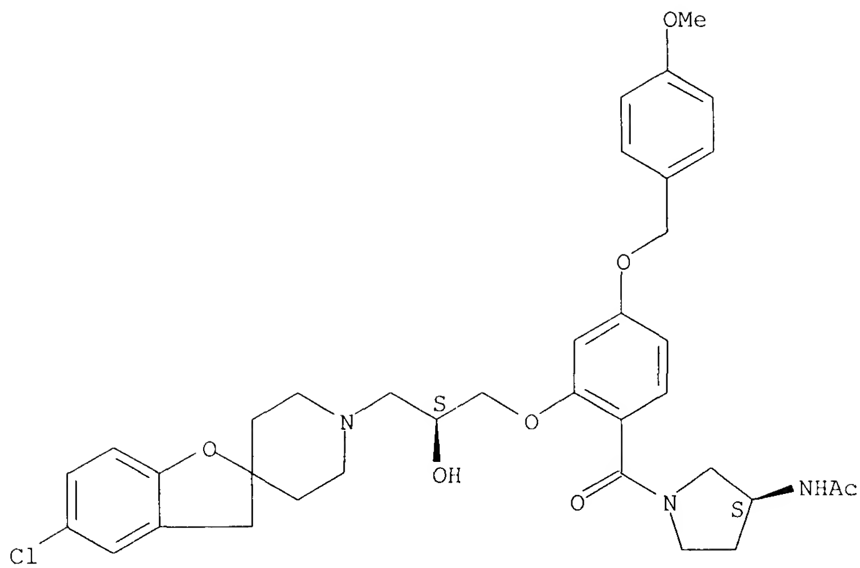
RN 644970-20-7 CAPLUS
CN Benzoic acid, 4-fluoro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



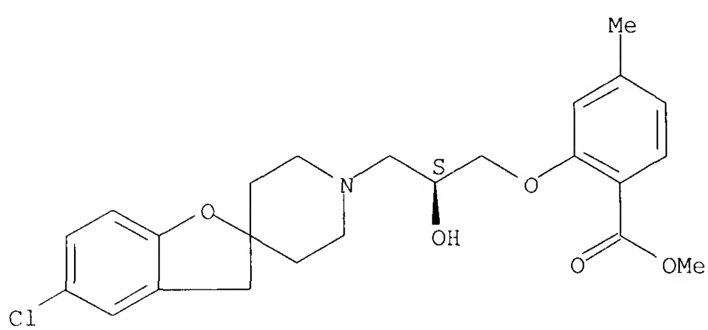
RN 644970-23-0 CAPLUS
CN Acetamide, N-[(3S)-1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-3-pyrrolidinyl]- (CA INDEX NAME)

Absolute stereochemistry.



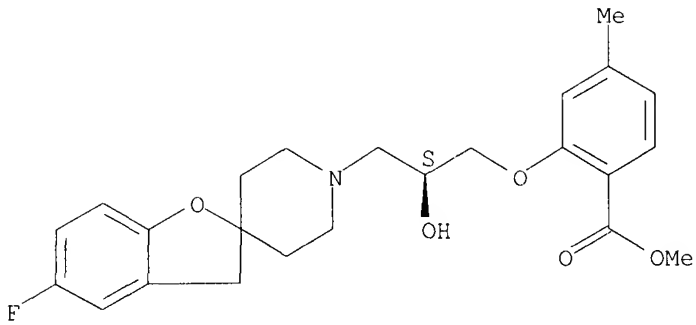
RN 644970-26-3 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methyl-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



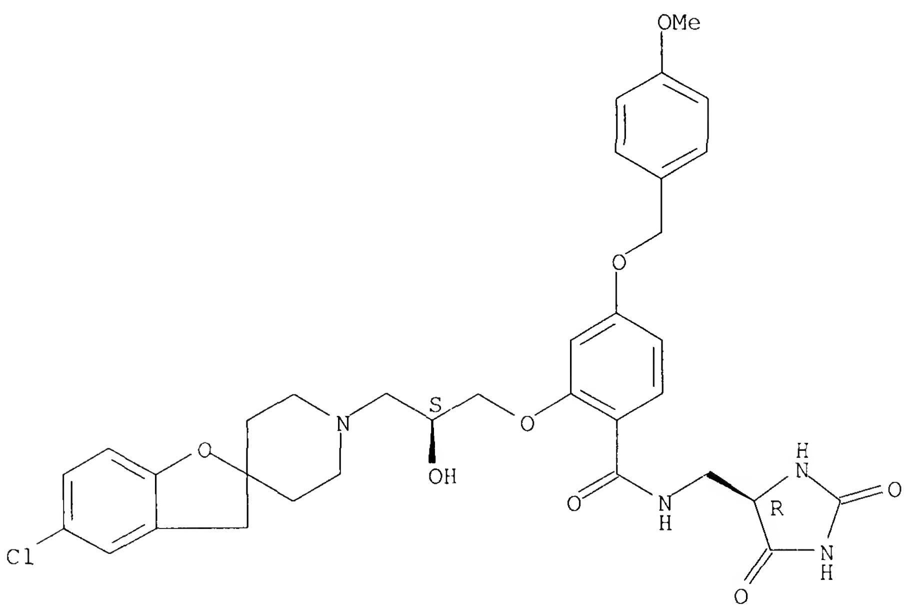
RN 644970-29-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-methyl-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



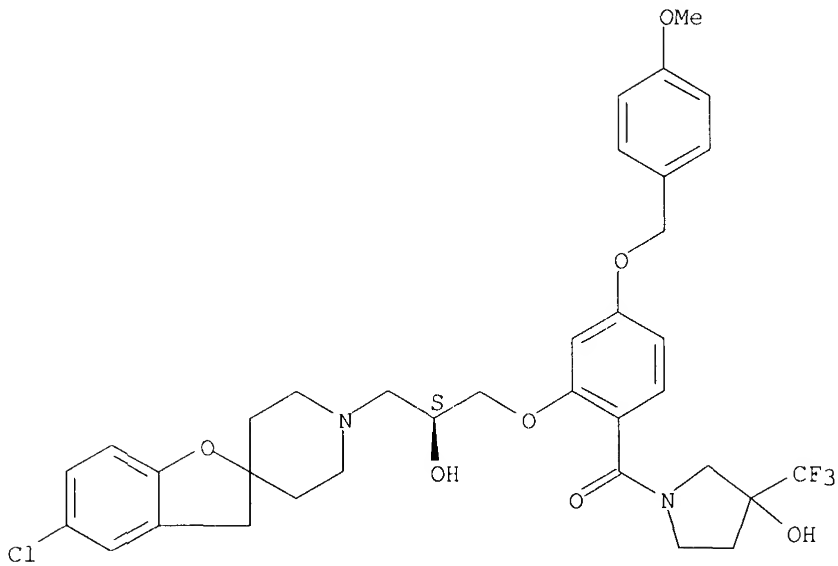
RN 644970-33-2 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-[[(4R)-2,5-dioxo-4-imidazolidinyl]methyl]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



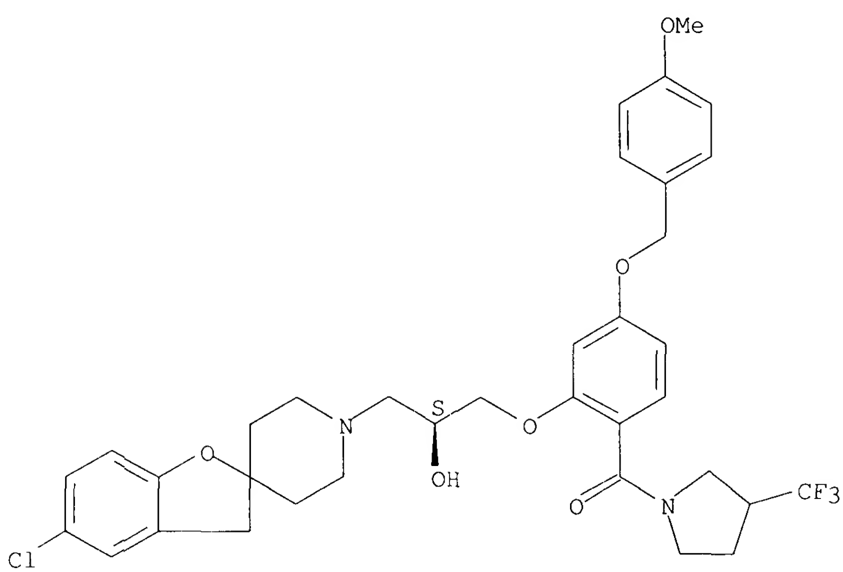
RN 644970-38-7 CAPLUS
CN 3-Pyrrolidinol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



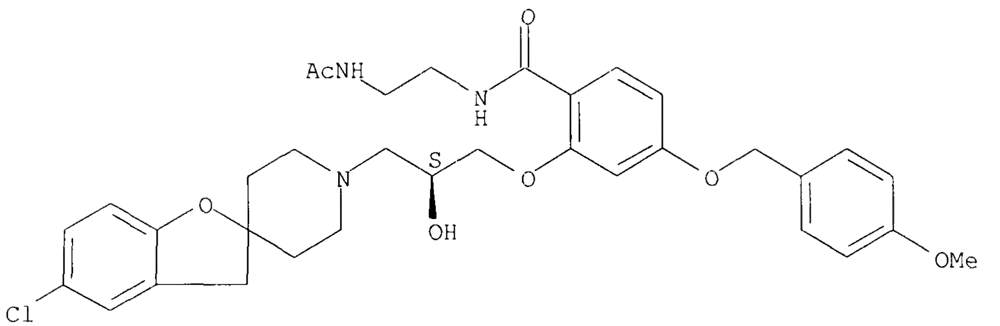
RN 644970-43-4 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-3-(trifluoromethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



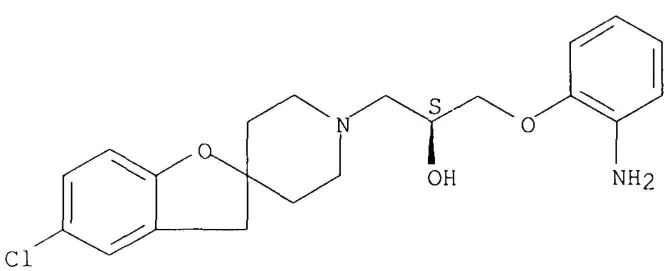
RN 644970-45-6 CAPLUS
CN Benzamide, N-[2-(acetylamino)ethyl]-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644970-57-0 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-aminophenoxy)methyl]-5-chloro-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



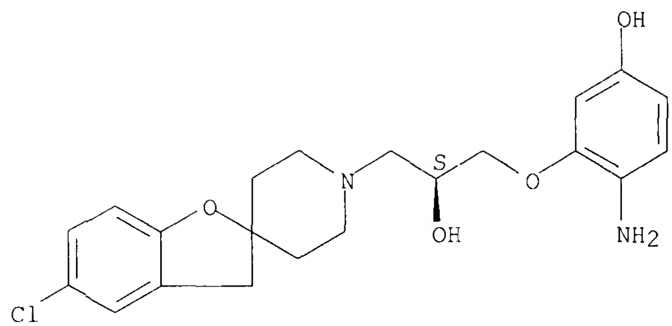
●2 HCl

RN 644970-61-6 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-amino-5-hydroxyphenoxy)methyl]-5-chloro-, (αS)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

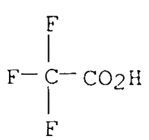
CRN 644970-60-5
CMF C21 H25 Cl N2 O4

Absolute stereochemistry.



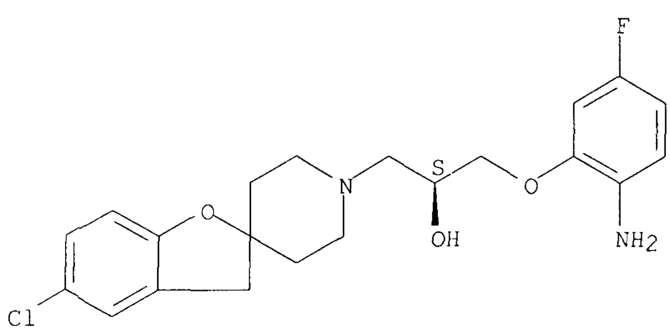
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644970-64-9 CAPLUS
CN Spiro[benzofuran-2(3H),4'-piperidine]-1'-ethanol, α-[(2-amino-5-fluorophenoxy)methyl]-5-chloro-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)

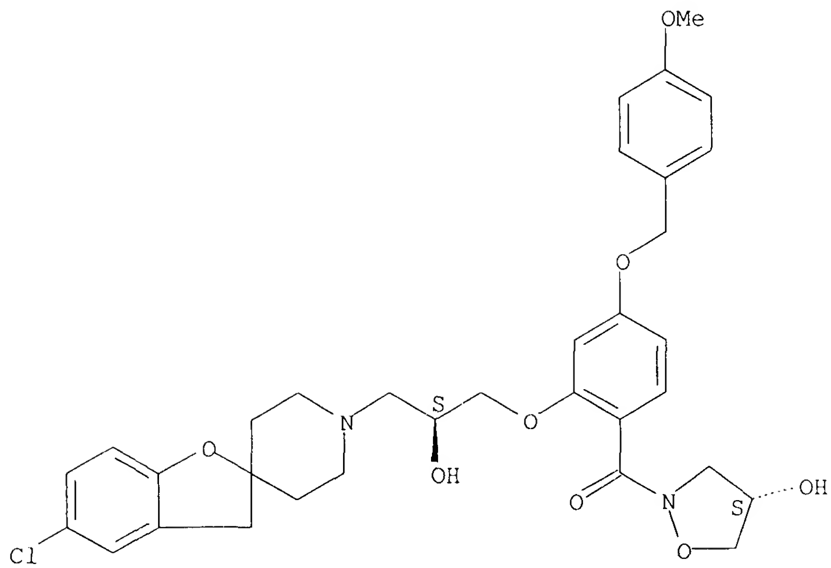
Absolute stereochemistry.



●2 HCl

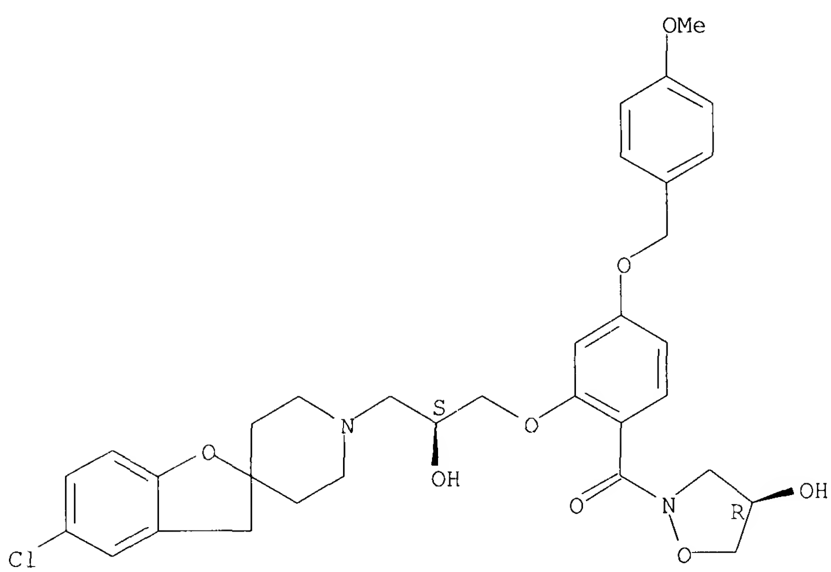
RN 644970-69-4 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



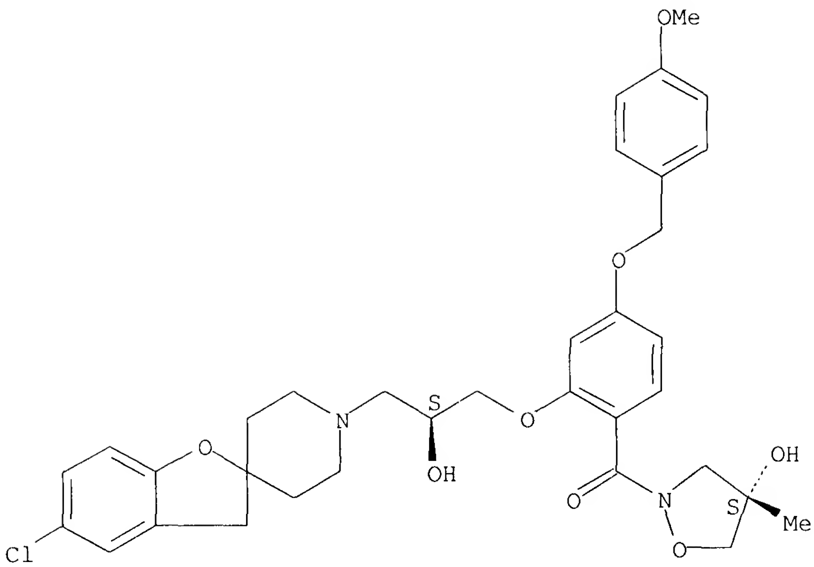
RN 644970-73-0 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



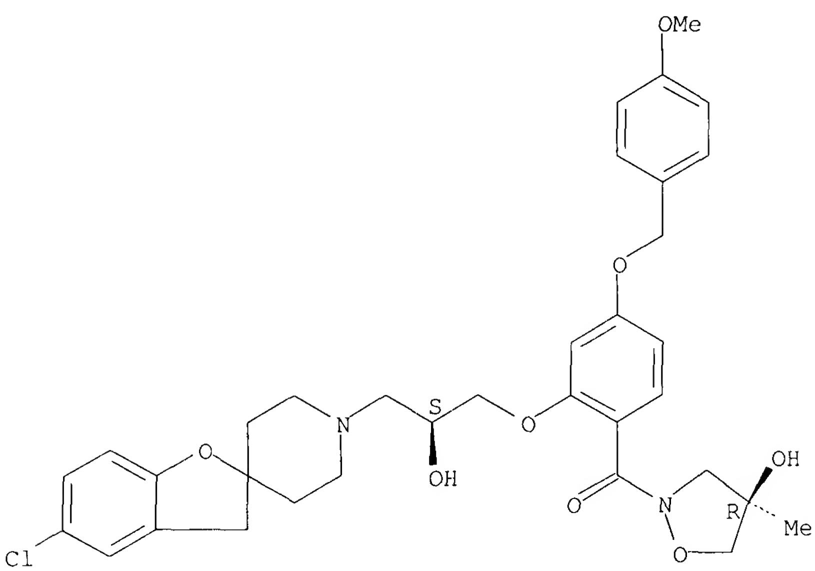
RN 644970-80-9 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-4-methyl-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



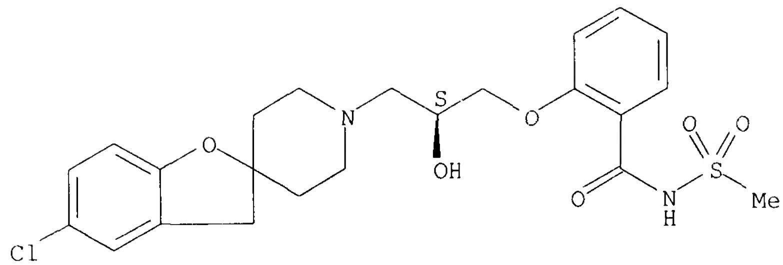
RN 644970-86-5 CAPLUS
CN 4-Isoxazolidinol, 2-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-4-methyl-, (4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



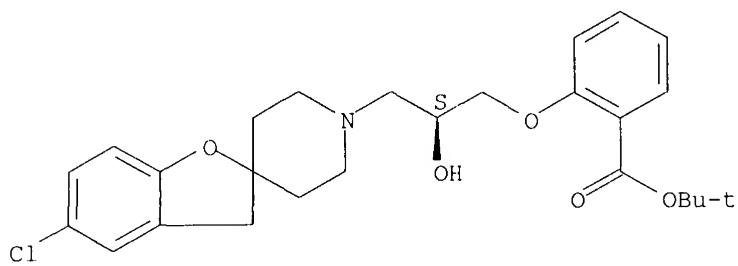
RN 644970-87-6 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(methylsulfonyl)- (CA INDEX NAME)

Absolute stereochemistry.



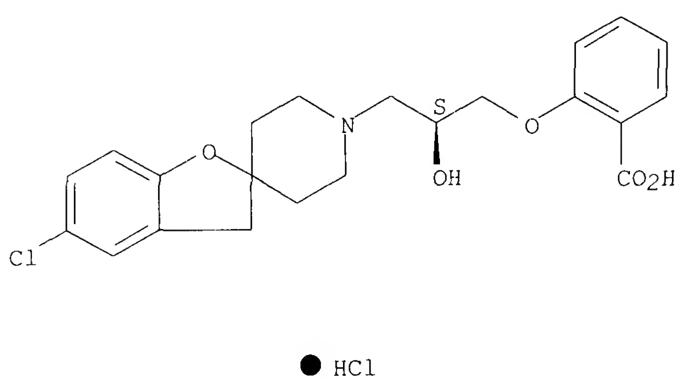
RN 644970-90-1 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.



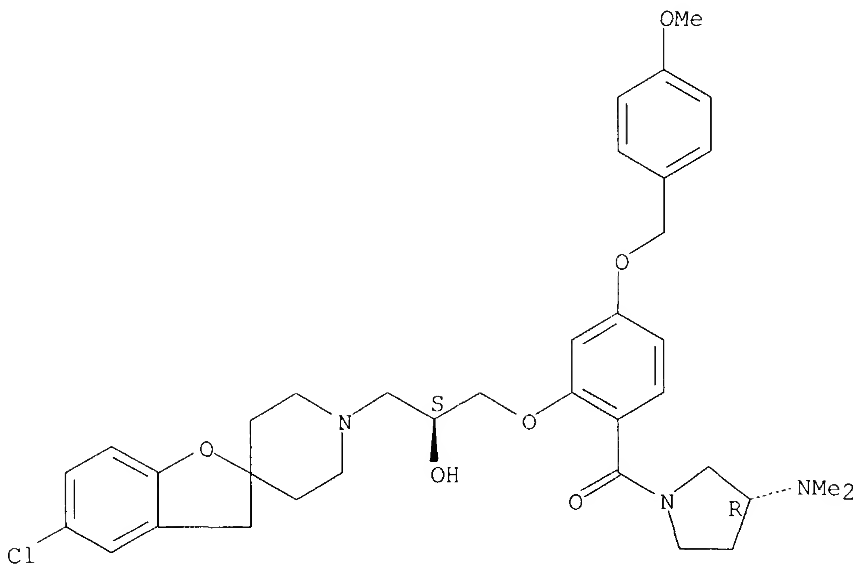
RN 644970-95-6 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



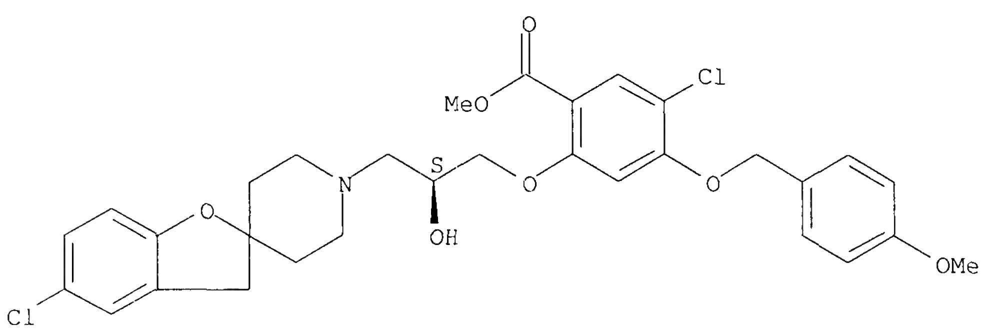
RN 644970-96-7 CAPLUS
CN 3-Pyrrolidinamine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-N,N-dimethyl-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-07-3 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.

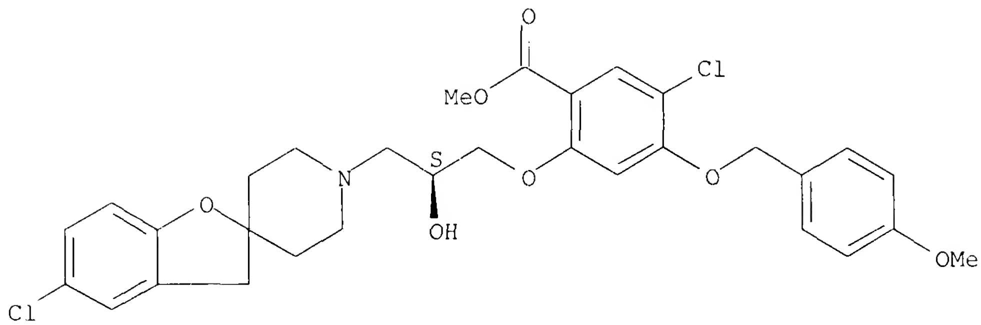


RN 644971-08-4 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

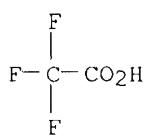
CRN 644971-07-3
CMF C31 H33 Cl2 N O7

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

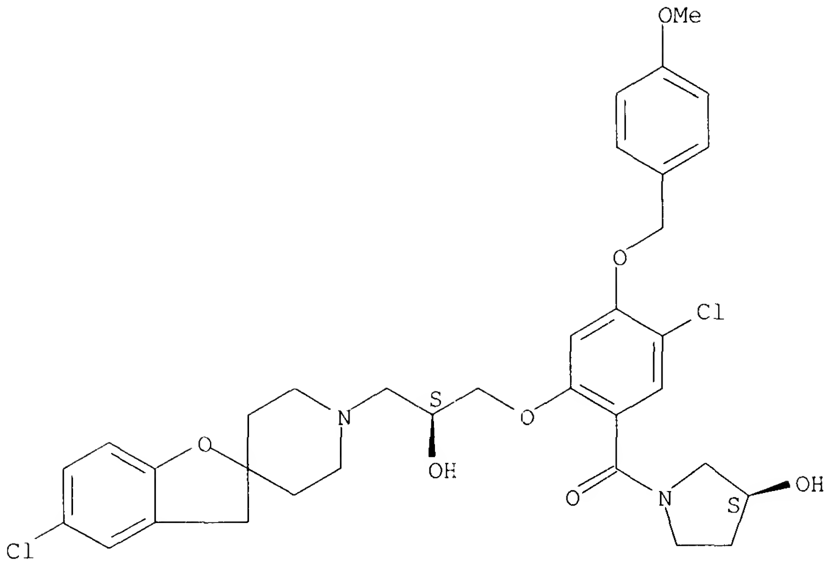


RN 644971-11-9 CAPLUS
CN 3-Pyrrolidinol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (3S)-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

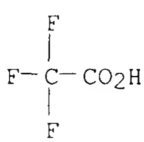
CRN 644971-10-8
CMF C34 H38 Cl2 N2 O7

Absolute stereochemistry.



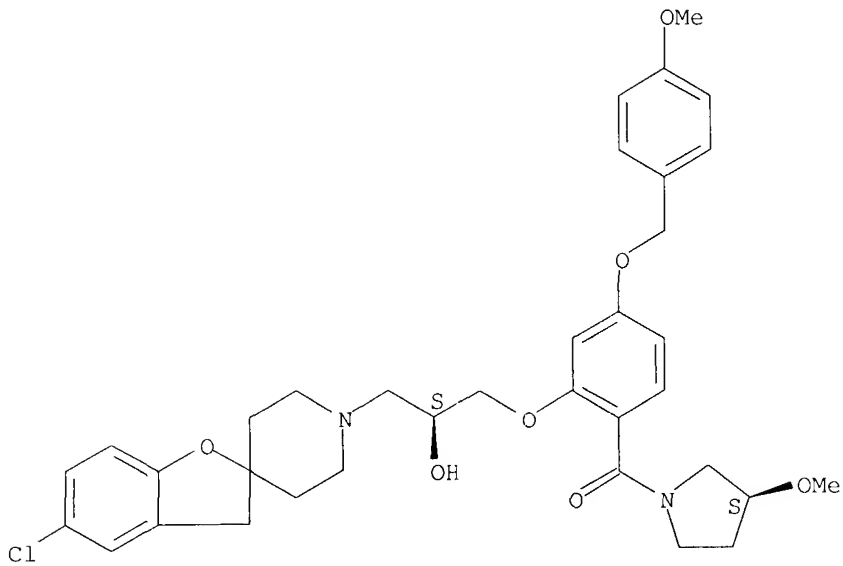
CM 2

CRN 76-05-1
CMF C2 H F3 O2



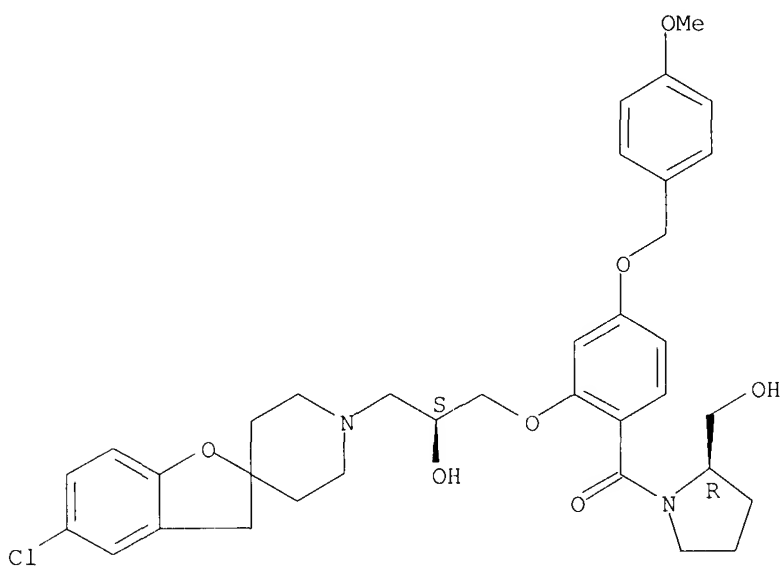
RN 644971-14-2 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-3-methoxy-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-17-5 CAPLUS
CN 2-Pyrrolidinemethanol, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644971-25-5 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry.

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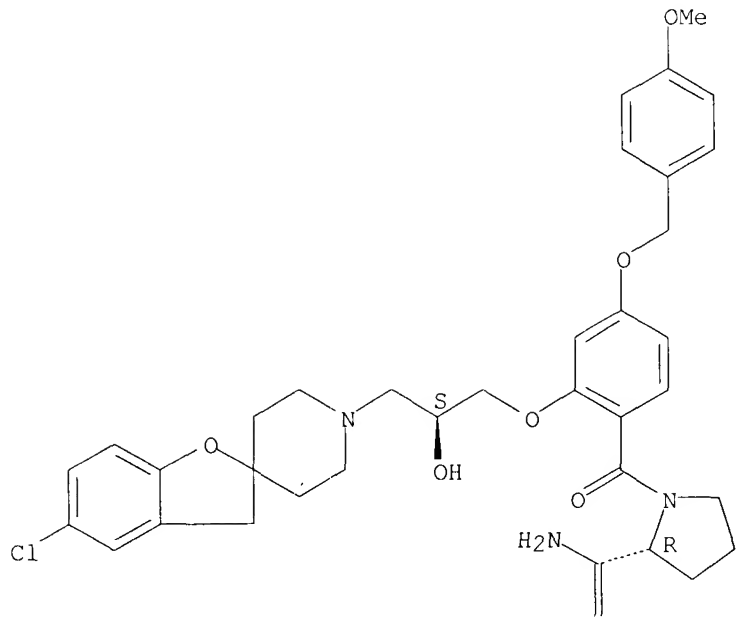

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RN 644971-41-5 CAPLUS

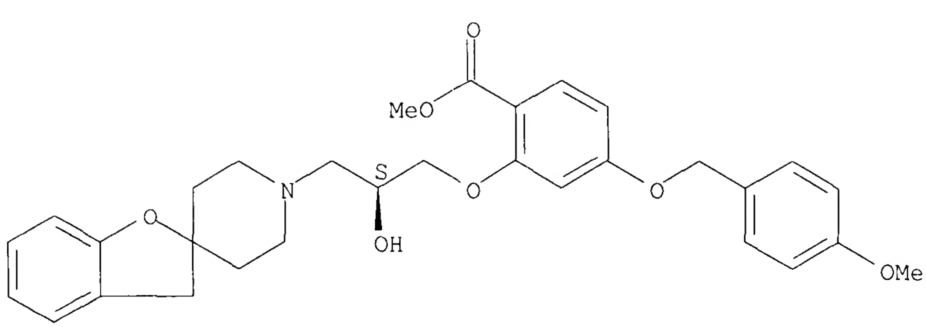
CN Benzoic acid, 2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 644971-40-4

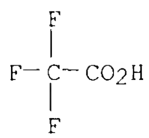
CMF C31 H35 N O7

Absolute stereochemistry.



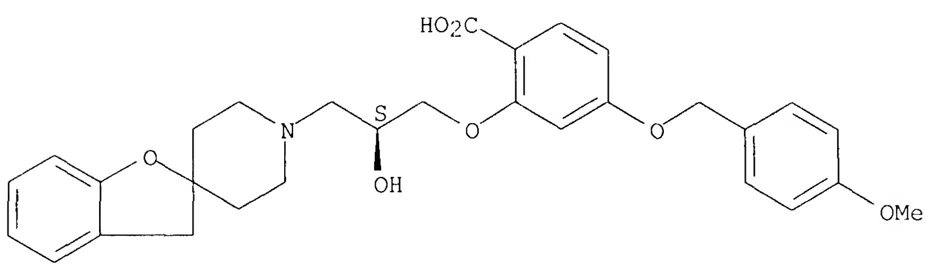
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 644971-42-6 CAPLUS
CN Benzoic acid, 2-[(2S)-2-hydroxy-3-spiro[benzofuran-2(3H),4'-piperidin]-1'-ylpropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



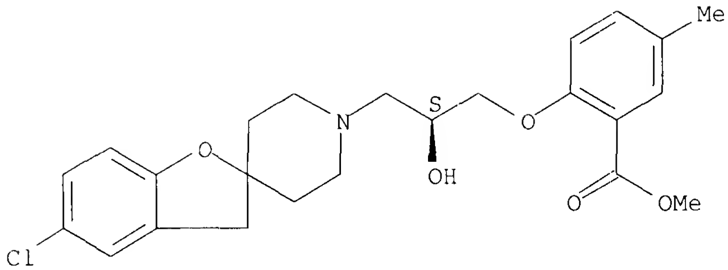
● HCl

RN 644971-46-0 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-5-methyl-, methyl ester, trifluoroacetate (salt) (9CI) (CA INDEX NAME)

CM 1

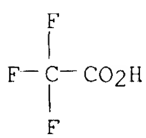
CRN 644971-45-9
CMF C24 H28 Cl N O5

Absolute stereochemistry.



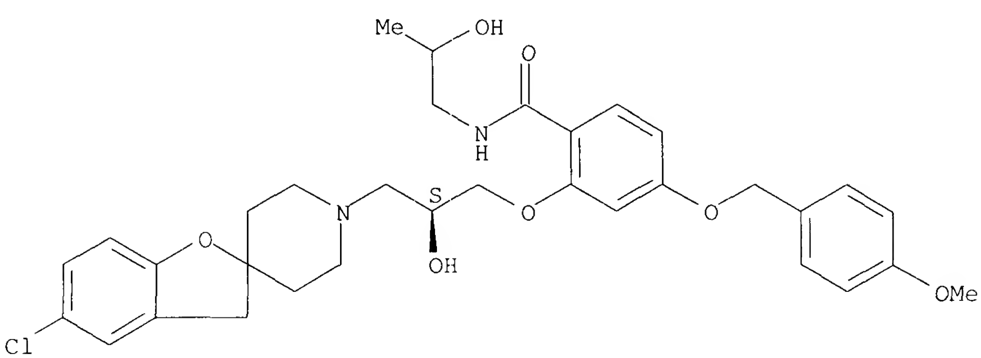
CM 2

CRN 76-05-1
CMF C2 H F3 O2



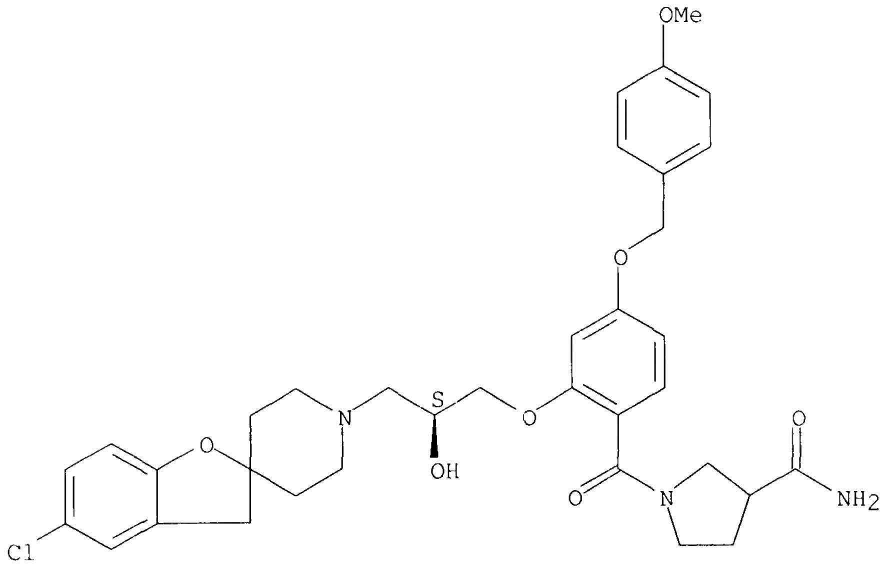
RN 644971-67-5 CAPLUS
CN Benzamide, 2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-N-(2-hydroxypropyl)-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644972-56-5 CAPLUS
CN 3-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 644972-60-1 CAPLUS
CN 2-Pyrrolidinecarboxamide, 1-[2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry.

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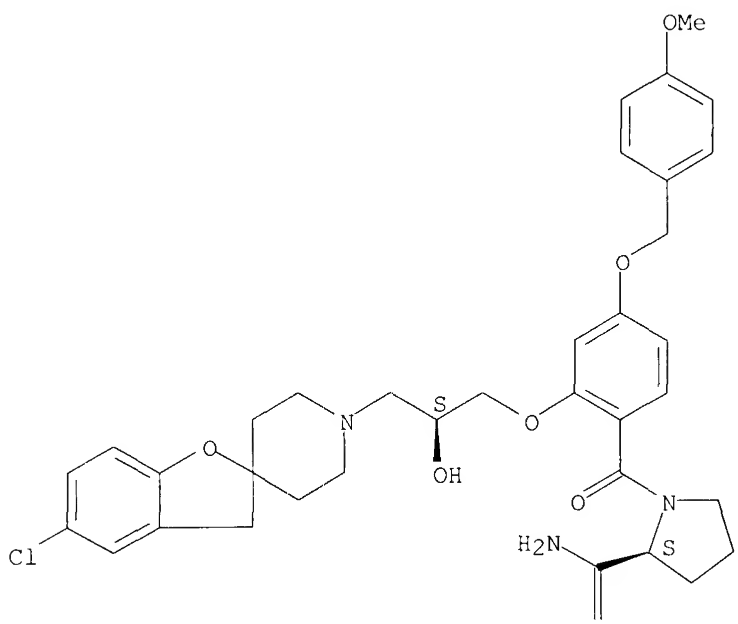

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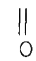
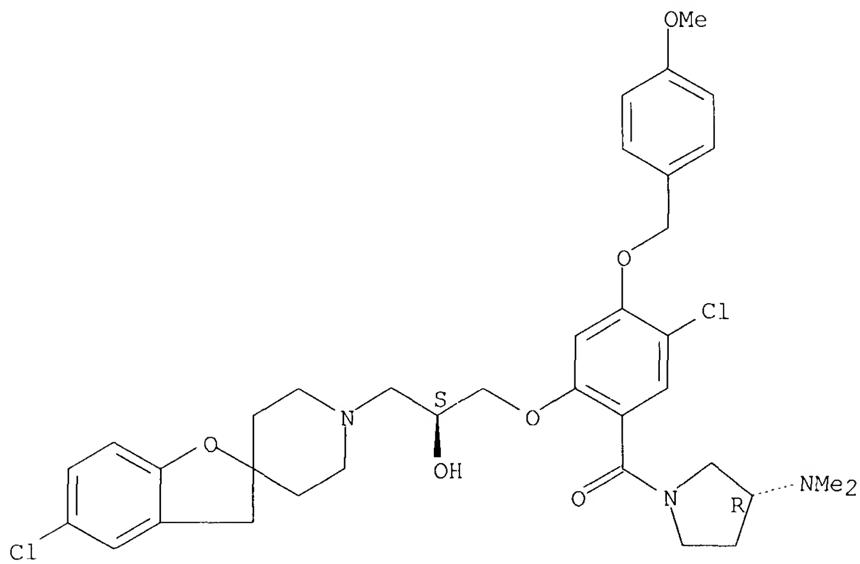


RN 644972-64-5 CAPLUS

CN 3-Pyrrolidinamine, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-N,N-dimethyl-, (3R)- (9CI) (CA INDEX NAME)

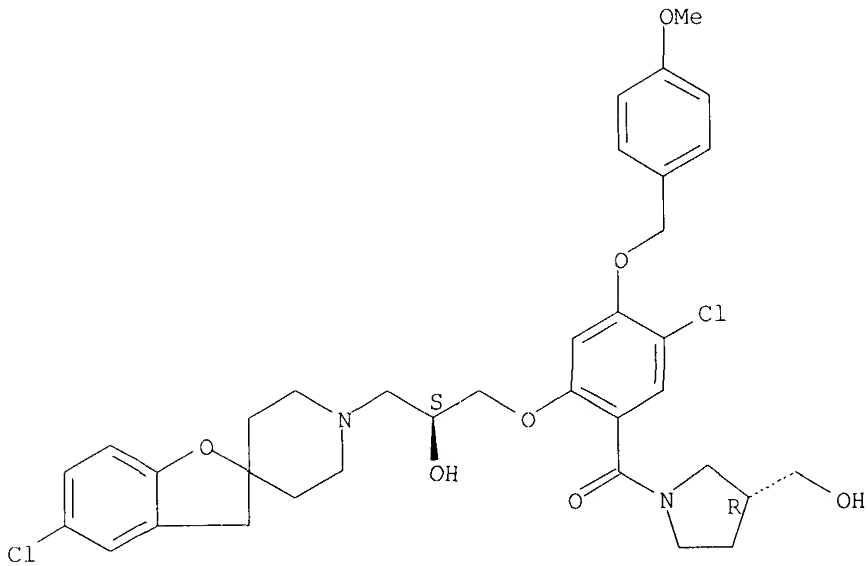
Absolute stereochemistry.



RN 644972-67-8 CAPLUS

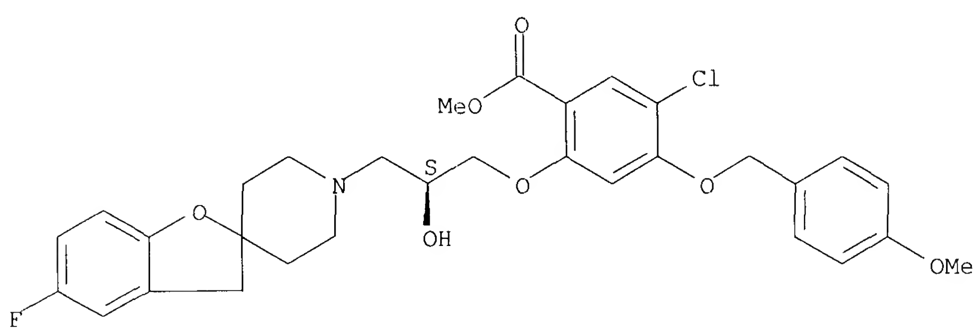
CN 3-Pyrrolidinemethanol, 1-[5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



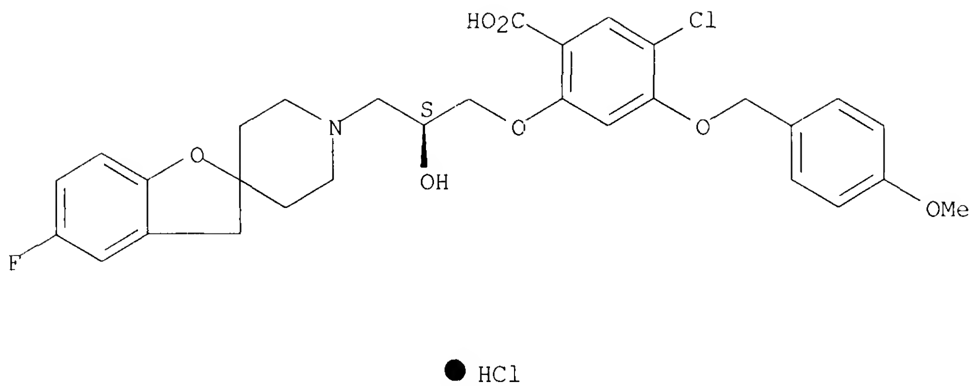
RN 644972-72-5 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



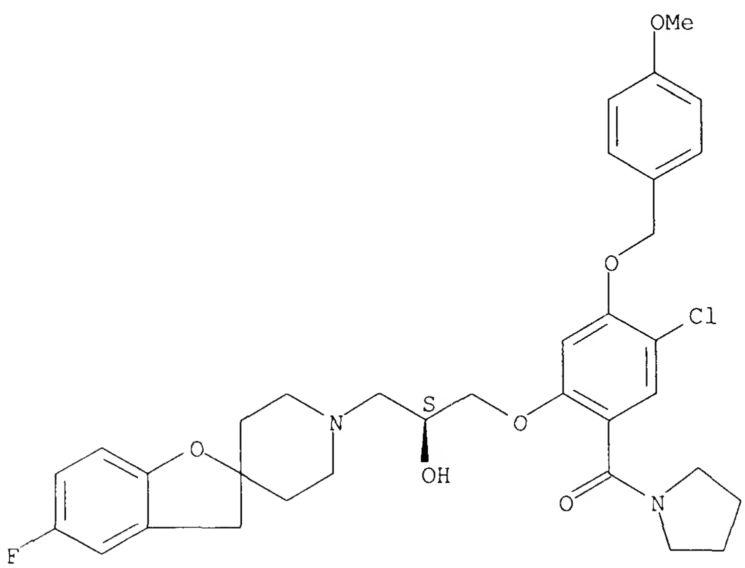
RN 644972-73-6 CAPLUS
CN Benzoic acid, 5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



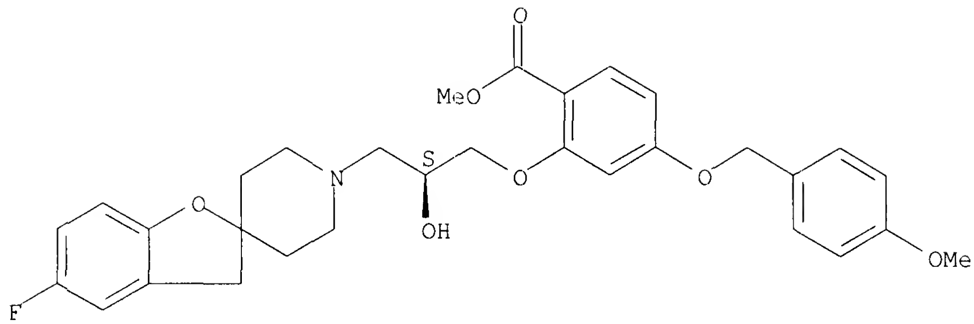
RN 644972-74-7 CAPLUS
CN Pyrrolidine, 1-[5-chloro-2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



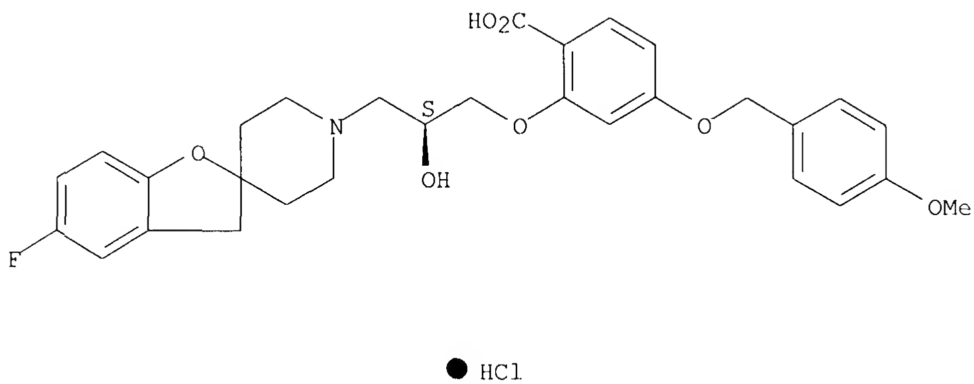
RN 644972-83-8 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



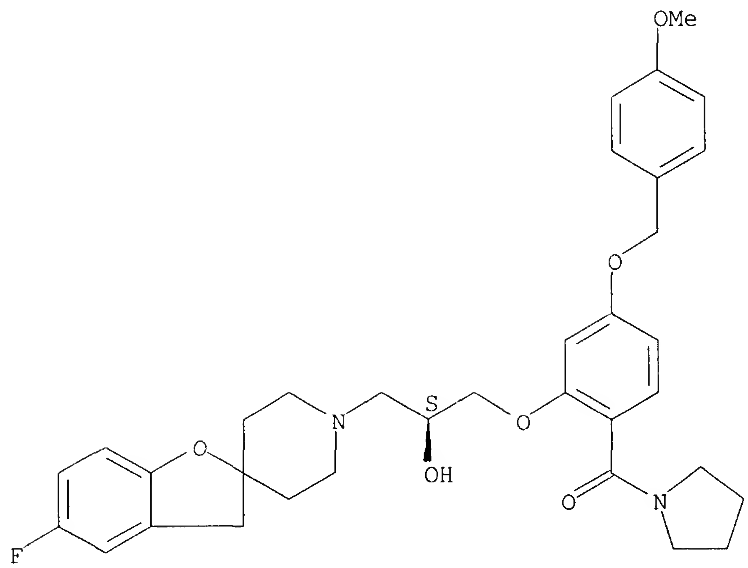
RN 644972-84-9 CAPLUS
CN Benzoic acid, 2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

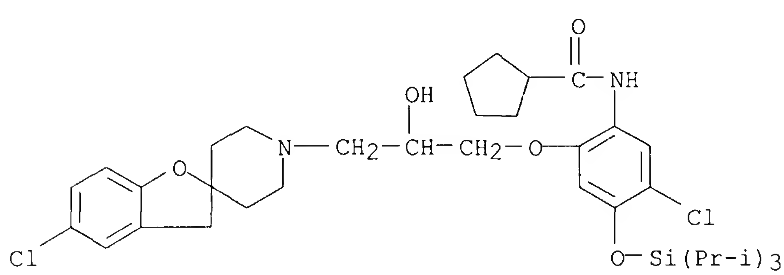


RN 644972-85-0 CAPLUS
CN Pyrrolidine, 1-[2-[(2S)-3-(5-fluorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 644972-91-8 CAPLUS
CN Cyclopentanecarboxamide, N-[5-chloro-2-[3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[[tris(1-methylethyl)silyl]oxy]phenyl]- (CA INDEX NAME)



RN 644973-04-6 CAPLUS
CN Benzoyl azide, 5-chloro-2-[(2S)-3-(5-chlorospiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-2-hydroxypropoxy]-4-[(4-methoxyphenyl)methoxy]- (CA INDEX NAME)

Absolute stereochemistry.

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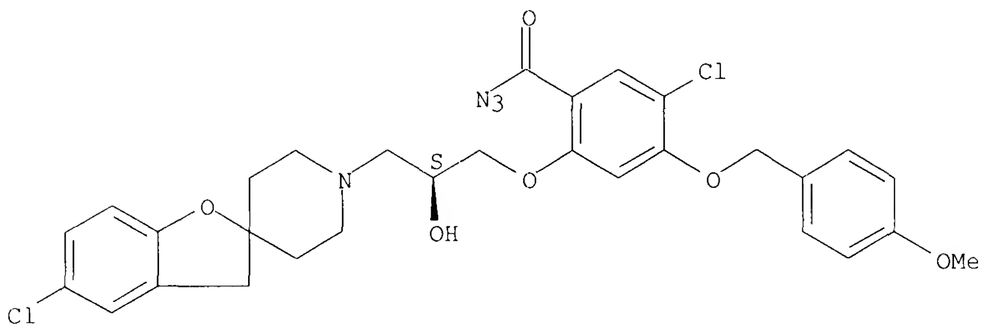
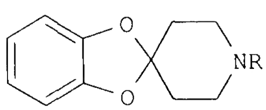


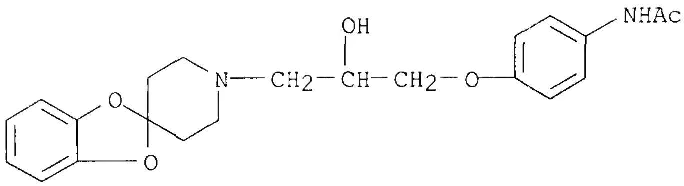
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:736623 CAPLUS
DOCUMENT NUMBER: 126:89321
TITLE: Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines]
AUTHOR(S): Pujol, M. D.; Rosell, G.; Guillaumet, G.
CORPORATE SOURCE: Fac. Farm., Univ. Barcelona, Barcelona, 08028, Spain
SOURCE: European Journal of Medicinal Chemistry (1996), 31(11), 889-894
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

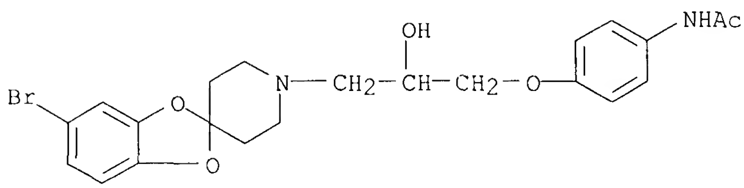


I

AB The synthesis of a new series of spiropiperidines is reported. Some of these compds. showed interesting adrenergic activity. The biol. activities of the new compds. were evaluated on guinea pig atria (β1), guinea-pig trachea (β2), and rat vas deferens (α). Three of the compds., e.g. I [R = CH2CH(OH)CH2OC6H4NHCOMe-4], showed activity comparable to propranolol, in spite of being tertiary amines.
IT 185316-89-6P 185316-99-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines])
RN 185316-89-6 CAPLUS
CN Acetamide, N-[4-(2-hydroxy-3-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-ylpropoxy)phenyl]- (9CI) (CA INDEX NAME)



RN 185316-99-8 CAPLUS
CN Acetamide, N-[4-[3-(5-bromospiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropoxy]phenyl]- (CA INDEX NAME)



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L1                STRUCTURE UPLOADED
L2              1 S L1
L3             13 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 16:03:45 ON 10 MAR 2008
L4              2 S L3

     FILE 'REGISTRY' ENTERED AT 16:05:38 ON 10 MAR 2008
L5                STRUCTURE UPLOADED
L6             34 S L5
L7            436 S L5 FULL

     FILE 'CAPLUS' ENTERED AT 16:08:30 ON 10 MAR 2008
L8              5 S L7

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L5 HAS NO ANSWERS
L5                STR
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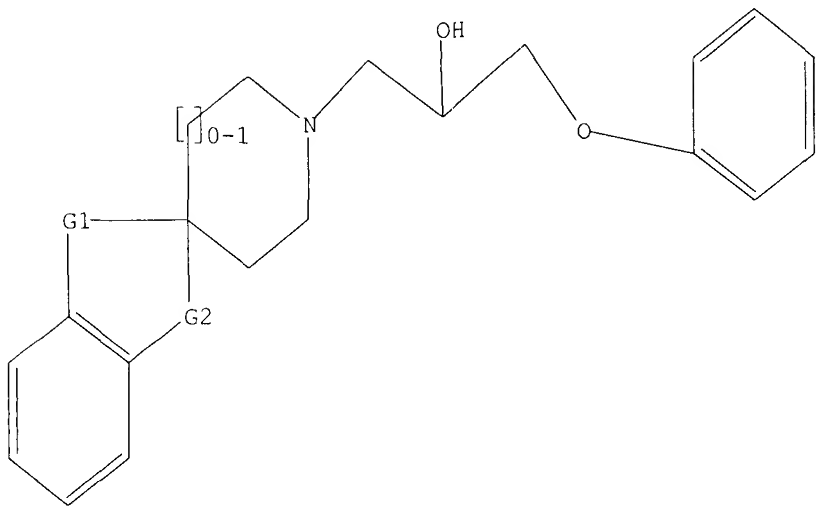
10/579,545



G1 C,O
G2 C,O,N

Structure attributes must be viewed using STN Express query preparation.

=>

Attorney's Docket No.: 06275-510US1 / 101279-1P US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Andrew Baxter et al.	Art Unit	: Unknown
Serial No.	: 10/579,545	Examiner	: Unknown
Filed	: May 16, 2006	Conf. No.	: 3967
Title	: NOVEL COMPOUNDS		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references listed on the attached PTO-1449 form. Under 37 C.F.R. § 1.98 (a)(2)(ii), only copies of foreign patent documents and/or non-patent literature are enclosed. Copies of any listed U.S. patents or U.S. patent application publications can be provided upon request. Copies of International Search Reports for WO 2004/005295, WO 2005/037814, WO/2005/040167, WO 2005/054249 and WO/2005/061499 are also enclosed.

Applicants provide a listing below of commonly owned co-pending U.S. patent applications that are included on the PTO-1449. Please note that the commonly owned co-pending U.S. patent applications were filed as U.S. national phase patent applications under 35 U.S.C. §371, and therefore the listing includes a reference to the PCT publication number for each of commonly owned co-pending U.S. patent applications.

The PTO-1449 lists the commonly owned co-pending U.S. patent applications by their corresponding published PCT publication numbers. The published U.S. patent applications are listed on the PTO-1449 under both the U.S. publication numbers and the PCT publication numbers.

U.S. Patent Application Serial No./ Published U.S. Patent Application	Corresponding Published PCT Patent Application
US-2005-0245741-A1	WO 2004/005295 (previously cited in 5/16/06 IDS)
US 2007-0021498-A1	WO 2005/037814
10/575,525	WO 2005/040167
10/581,171	WO 2005/054249
10/583,468	WO 2005/061499

This statement is being filed before the receipt of a first Office Action on the merits. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-510US1.

Respectfully submitted,

Date: March 8, 2007

Catherine M. McCarty Reg. No. 54,301
for Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21579871.doc

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-510US1	Application No. 10/579,545
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Andrew Baxter et al.	
	Filing Date May 16, 2006	Group Art Unit Unknown

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	4,010,201	03/01/1977	Lednicer			
	AB	4,263,317	04/21/1981	Martin et al.			
	AC	US-2005-0245741-A1	11/03/2005	Hossain et al.			
	AD	US 2007-0021498 A1	01/25/2007	Hossain			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	AE	EP 0004952	10/31/1979	Europe			Abstract	
	AF	EP 0417631	03/20/1991	Europe			Abstract	
	AG	EP 0722941	07/24/1996	Europe				
	AH	EP 1061076	12/20/2000	Europe				
	AI	WO 92/10096	06/25/1992	WIPO				
	AJ	WO 96/36625	11/21/1996	WIPO				
	AK	WO 01/30780	05/03/2001	WIPO				
	AL	WO 02/102387	12/27/2002	WIPO				
	AM	WO 03/037271	05/08/2003	WIPO				
	AN	WO 2005/037814	04/28/2005	WIPO				
	AO	WO 2005/040167	05/06/2005	WIPO				
	AP	WO 2005/054249	06/16/2005	WIPO				
	AQ	WO 2005/061499	07/07/2005	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AR	Mehrotra et al., "Spirocyclic Nonpeptide Glycoprotein IIb-IIIa Antagonists. Part 3: Synthesis and SAR of Potent and Specific 2,8-Diazaspiro[4.5]decanes", Bioorganic & Medicinal Chemistry Letters 12:1103-1107 (2002)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CA/

Examiner Signature	Date Considered
/Charanjit Aulakh/	03/11/2008

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

10/579545

Attorney's Docket No.: 06275-510US1 / 101279-1P US

IAP20 Rec'd PCT/PTO 17 MAY 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Andrew Baxter et al.	Art Unit	: Unknown
Serial No.	: To Be Assigned	Examiner	: Unknown
Filed	: Herewith		
Title	: NOVEL COMPOUNDS		

MAIL STOP PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references listed on the attached PTO-1449 form. A copy of a communication from a foreign patent office in a counterpart application is also enclosed.

This statement is being filed with the application. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-510US1.

Respectfully submitted,

Date: May 16, 2006

Catherine M. McCarty Reg. No. 54,301
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21324301.doc

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL 980076416 US

May 16, 2006
Date of Deposit

IAP20 Rec'd PCT/PTO 13 MAY 2006

Sheet 1 of 1

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-510US1	Application No. To Be Assigned 10/579545
Information Disclosure Statement by Applicant (Use several sheets if necessary)	Applicant Andrew Baxter et al.	
(37 CFR §1.98(b))	Filing Date Herewith	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation	
							Yes	No
	AA	EP 0004951	10/31/1979	Europe				
	AB	WO 98/25605	06/18/1998	WIPO				
	AC	WO 98/31364	07/23/1998	WIPO				
	AD	WO 00/14086	03/16/2000	WIPO				
	AE	WO 01/64213 A1	09/07/2001	WIPO				
	AF	WO 2004/005295 A1	01/15/2004	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AG	Pujol et al., "Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro(1,3-benzodioxolopiperidines) and spiro(1,3-benzodioxanepiperidines)", *Eur J Med Chem* 31:889-894 (1996)
	AH	
	AI	
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	AN	
	AO	
	AP	
	AQ	
	AR	
	AS	
	AT	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /CA/

Examiner Signature	Date Considered
/Charanjit Aulakh/	03/11/2008

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.